BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 14 1959

PRESENT POSITION OF IMMUNIZATION AGAINST POLIOMYELITIS WITH LIVE VIRUS VACCINES*

BY

ALBERT B. SABIN, M.D.

Professor of Research Paediatrics, the Children's Hospital Research Foundation and University of Cincinnati College of Medicine, Cincinnati, Ohio

Immunization against poliomyelitis with orally administered live attenuated poliovirus vaccine presents special problems not previously encountered with other live virus vaccines employed in human beings, and it is entirely proper to approach it in the most cautious and critical manner. The recent communications (Dick and Dane, 1958 ; Dane *et al.*, 1958 ; Clarke *et al.*, 1958) and editorial comments (leading article, 1958) in the *British Medical Journal* did not take into account all the available published and unpublished data that were available to the writers, and, in my opinion, did not give a complete picture of the present status of our knowledge on this subject.

Accordingly I am prompted to bring up to date the information available to me on four topics that came under special consideration in the recent discussions: (1) neurotropism of viruses excreted by the vaccinated individuals and after further multiplication in contacts ; (2) persistence of antibody and its relation to resistance of the intestinal tract to reinfection ; (3) effect of multiple doses of Salk vaccine and of high levels of neutralizing antibody produced by killed virus vaccine on multiplication of poliovirus in the pharynx and intestines of children ; and (4) the present status of field trials with the large lots of the three types of vaccine that I prepared two years ago.

Problems in Estimation of Neurotropism of Polioviruses

In working out the quantitative aspects of neurotropism of various polioviruses for monkeys, and its relationship to the neurotropism of the same viruses for chimpanzees and, by inference based on epidemiological data, also for man, I found that the thalamic neurones of the monkey are more resistant than those in the lumbar enlargement of the spinal cord, and that the lumbar neurones of chimpanzees are much more resistant than those of monkeys (Sabin, 1956a, 1957a). Since the neurotropism of a poliovirus particle is in effect a measure of its capacity to multiply sufficiently in a given neurone to be able to spread to and destroy the large number of other neurones required to produce clinical manifestations, it is important not only to differentiate between the effect of 100 and 100,000 or 100,000,000 infective virus particles, but also to take into account the precise placement of the inoculum. During the past six years I have used certain techniques of intracerebral and intraspinal inoculation on thousands of monkeys which yielded sufficiently reproducible results to permit a fair quantitative estimate of neurotropism and gradation of strains (Sabin, 1956a, 1957b). Although I could have imagined, *a priori*, that certain variations in technique might yield different results, I did not realize until recently how important those differences could be in the estimation of both "cerebral" and "spinal" neurotropism.

*Aided by grants from the National Foundation for Infantile Paralysis.

"Cerebral" Neurotropism

In measuring "cerebral" neurotropism, one attemp.s to measure the capacity of poliovirus particles to multiply sufficiently in the neurones of the thalamus and adjacent susceptible regions to permit further progression along neural pathways to the motor neurones of the spinal cord, whose destruction in sufficient numbers to produce clinical paralysis serves as the final index of activity. If, however, the inoculum itself causes a sufficiently extensive traumatic lesion to lay open the tracts leading directly to the spinal cord, enough virus can invade the spinal neurones without the necessary preliminary multiplication in the susceptible cerebral neurones. Confirmation of such an event has been obtained by showing that the virus recovered from the spinal cord of such monkeys has no greater intracerebral activity than that used for the original inoculation (Sabin, 1955a).

Before tissue cultures became available, the technique of intracerebral inoculation that was most suitable for detecting minimal amounts of poliovirus involved the injection of 0.5-ml. quantities into each thalamic region (Bodian *et al.*, 1950). This technique produces extensive local damage and is often associated with varying clinical manifestations resulting from initial damage and subsequent inflammatory reaction in the tracts and adjacent regions ; it is also most likely to permit mechanical invasion of the spinal neurones, and is therefore not suitable for an estimate of "cerebral" neurotropism. This is the technique that was used by Clarke *et al.* (1958) in their tests on excreted virus, and by others. So long as the virus used has a very limited "spinal" neurotropism, this procedure will not give rise to spinal paralytic manifestations, although the interpretation of a paresis based on cerebral trauma and subsequent inflammation may be confused by the presence of limited focal, specific poliomyelitic lesions in

the spinal cord, which by themselves are insufficient to give rise to spinal paralytic manifestations. However, when a virus of greater "spinal" neurotropism is being tested this procedure is most likely to give rise to misleading results.

In my own work with viruses of low "spinal" activity, I have usually inoculated 1 ml. into the right thalamic region, which is less traumatic than 0.5 ml. given into each side, but still is not infrequently associated with traumatic hemiparesis, or hemiplegia, or a lower facial paralysis of the cerebral type. For all the cerebral tests on excreted virus that I reported previously, I used only 0.5 ml. on one side. Since it is possible to inoculate 10 million or more tissue culture infective doses in a volume of 0.2 ml. some have suggested that a still smaller inoculum might be preferable. The danger in decreasing the volume too much is that one might more readily miss the thalamic region. Although the practice of inserting a 2.5-cm. 24-gauge needle about 6 mm. from the midline along the coronal suture usually places the inoculum in the right place, this is not an invariable guide. It is most important to pull back on the piston of the syringe to make sure that ventricular fluid is not obtained prior to inoculation and that the inoculum cannot be pulled back after inoculation; if the latter occurs it is important to change the position of the needle and reinoculate until it is evident that the fluid has diffused in the brain tissue and cannot be recovered.

Another worth-while precaution for avoiding unnecessary trauma is to inject slowly and not create a jet stream by forceful ejection of the fluid. It should also be stressed that an erroneous impression of lack of "cerebral" neurotropism might be obtained if the needle is inserted too far from the midline, and the inoculum is not placed in the vicinity of an area containing neurones that are susceptible to polioviruses.

In testing for cerebral neurotropism it is also important to remember that in mixed populations of virus particles the undiluted culture fluid may yield negative results, while paralysis may show up in the animals inoculated with diluted material (Sabin *et al.*, 1954; Sabin, 1955a). In 1953 I demonstrated such interference experimentally by inoculating a mixture of 100,000 tissue culture infective doses of an attenuated type I virus with 10 intracerebrally paralytic doses of the virulent Mahoney virus. Only 4 of the 10 monkeys inoculated with the mixture developed paralysis, while all 5 receiving the small dose of Mahoney virus succumbed and all 9 receiving only the attenuated virus remained well.

In interpreting the results of an intracerebral inoculation, particularly when only a small proportion of the inoculated monkeys exhibit spinal paralysis, with quantitatively compatible specific lesions, one must also keep in mind not only that the monkey nervous system acts as a selective medium for the small proportion of more neurotropic virus particles that may be present in a large population, but also that more neurotropic mutants, sometimes strict neurotropic mutants, not originally present in the inoculated material, may arise during the course of viral multiplication in the brain (Sabin, 1955a). I have observed this repeatedly and reported it on several occasions, particularly with viruses which may still multiply to a certain extent in the cerebral neurones.

Tests in tissue culture reveal the presence of strict neurotropic mutants, either by the failure of isolating cytopathogenic virus from the spinal cord, or by the zone phenomenon in which a 10% extract of the spinal cord produces no cytopathogenic effect or a very delayed one, while higher dilutions produce a rapid effect. Abortive infections have also been encountered in which the spinal cord has no demonstrable virus by passage either in tissue culture or in intracerebrally or intraspinally inoculated monkeys. It is noteworthy that I have not observed any of these phenomena, pointing to mutation in the nervous system of the monkey, in large numbers of monkeys that were inoculated intracerebrally with the strains of limited spinal activity that I finally selected for inclusion in the vaccine to be used for more extensive trials in man (Sabin, 1957b).

"Spinal" Neurotropism

The measure of "spinal" neurotropism is also not a measure of an "all or none" property, but of the varying capacity of poliovirus particles to multiply sufficiently in the motor neurones at the site of inoculation in the spinal cord to permit spread to the large enough number of contiguous neurones required for the production of various degrees of paralysis. It is well known that a muscle, indeed an individual muscle fibre, receives its motor innervation from neurones at multiple levels in the spinal cord, and that rather extensive lesions can be produced mechanically or specifically by virus action, without noticeably affecting the capacity of a muscle to function, if these lesions are not widely distributed over many levels. Thus, the requirements of this method are, on the one hand, to place the inoculum close enough to the motor cells to be infected, and, on the other hand, to avoid the traumatic destruction, by the initial disintegration of tissue and subsequent inflammatory response, of so many neurones that the further specific viral attack on a relatively small number of additional neurones will be sufficient to produce clinical manifestations varying from weakness to complete paralysis. The problem here is quite different from that involved in searching for an isolated particle of virulent virus in the safety testing of a killed-virus vaccine, where volumes as large as 0.5 ml. are purposely inoculated in a manner to produce traumatic paralysis in most of the monkeys, because the effect is then usually evident by the subsequent extensive spread of the paralysis.

The method that I have used in the past six years has permitted the demonstration of different grades of "spinal" neurotropism in strains of poliovirus that were completely or almost completely devoid of "cerebral" neurotropism for the monkey. It was the basis of all the work over a period of several years by which many strains were eliminated and only a few retained as candidates for a vaccine, ultimately designed to be tested on a large scale (Sabin, 1956a, 1957a, 1957b). Viruses which in small doses regularly produced paralysis after spinal inoculation by the method that I used obviously were capable of greater spread to other neurones than those that would do so only after inoculation of a 1,000 to 10,000 times larger dose. The viruses that I finally selected had such limited spinal activity, by this method of inoculation, that even amounts in the range of 1 million or 10 million tissue culture infective doses failed in most monkeys to produce any paralysis and in occasional ones even failed to produce specific lesions. However, the majority of clinically well monkeys showed limited focal specific lesions, indicating that the viruses multiplied to a limited extent, but in an

abortive fashion which prevented involvement of the large numbers of neurones required for the production of clinical manifestations. In chimpanzees these same viruses in about 10 million tissue culture infective doses produced neither paralysis nor lesions after inoculation into the grey matter of the lumbar cord.

During recent months it became apparent to me, however, that "die Methode ist alles," and I therefore find it necessary to describe in some detail the method that I used and to indicate how certain variations can, on the one hand, give rise to an erroneous impression of low or absent "spinal" neurotropism, and, on the other, to an impression of much greater neurotropism. By dissection and by inoculation of dyes, I decided that in monkeys the lumbar enlargement can be located by counting the four spaces between the spinous processes that lie above the level of the iliac crests (see Fig. 1). This fourth space corresponds also to the first space below the level of the last rib, and this may be used in checking the exact position. In training people I find that they most frequently mistake the third space for the fourth, which, as I shall show later, turns out to be crucial. The lumbar cord is so small and the interval between the spaces relatively so large, that a mistake in one space too low places the inoculum in the region of the lumbo-sacral conus, where it may readily diffuse into the roots rather than into the grey matter.

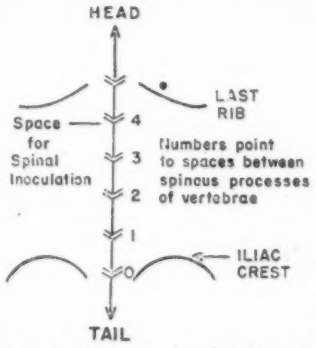


FIG. 1.—Diagram for location of lumbar enlargement of spinal cord of monkey where virus is inoculated for evaluation of "spinal neurotropism."

The monkey is tied on a board, face down, and a stiff cardboard roll (about 7.5 cm. in diameter) is placed under the abdomen to arch the back. I selected a 20-gauge needle (1.5 cm. long, short bevel) for inoculation simply because it was firm enough to penetrate the skin without bending on bony obstructions, but this also turns out to be important. The needle, attached to a tuberculin syringe, is passed through the fourth space, slightly to one side of the midline, until it hits the bone on the ventral aspect of the spinal canal, making certain that a contraction is observed in at least one group of muscles of one leg; if such a contraction or kick is not observed the needle is withdrawn and the procedure is repeated until a definite kick is observed. The needle is then withdrawn 1 to 2 mm. (depending on the size of the monkey) and 0.1 ml. is inoculated very slowly, without changing the position of the needle or attempting to produce additional muscle contractions. Great care is taken to avoid forcible injection which might give rise to a jet stream and greater disintegration of tissue. Even 0.1 ml. represents a large proportion of the total volume of the grey matter in the lumbar cord, and some of it must of necessity leak out around the cord or too much of the grey matter would be destroyed.

Figs. 2a and 3a show the type of lesions usually produced by the inoculum as seen 21 days after inoculation in monkeys, which at no time exhibited any signs of muscle weakness. The lumbar cord is cut at approximately 1-mm. intervals (one side being marked

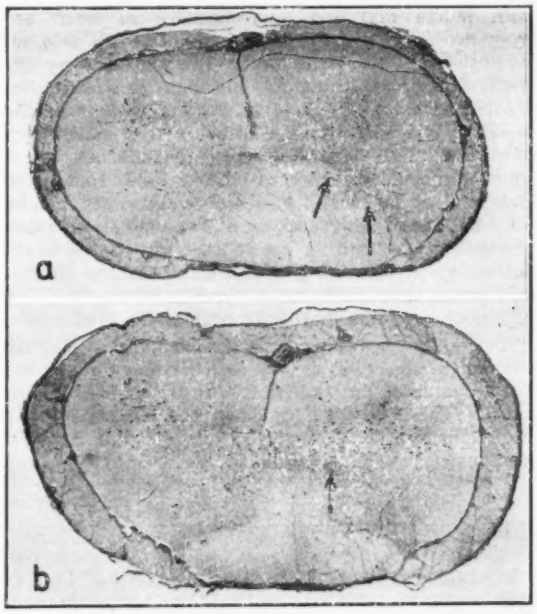


FIG. 2.—Lumbar cord of monkey inoculated intraspinally with 10^5 TCD_{50} of type 1, L Sc, 2 ab virus. (*a*) Arrows show inoculation scar leading into anterior horn, which shows no poliomyelitis lesions; (*b*) another level of lumbar cord with arrow pointing to residue of inoculum—note complete absence of inflammatory response or poliomyelitic lesions.

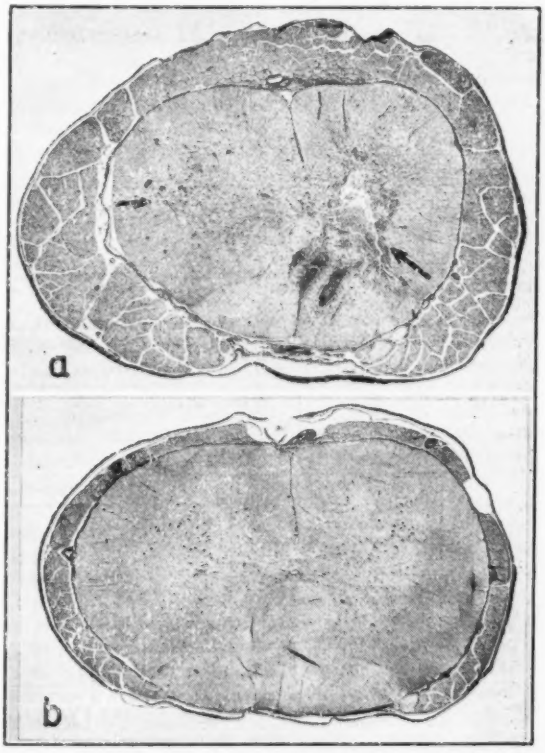


FIG. 3.—Lumbar cord of monkey inoculated intraspinally with 10^6 TCD_{50} of type 1, L Sc, 2 ab virus. (*a*) Arrow on right points to disintegration of tissue in posterior and anterior horns produced by inoculum, and arrow on left points to focal infiltration—note predominantly normal roots; (*b*) adjacent level of lumbar cord of same monkey—note complete absence of lesions.

with indian ink) and approximately 20 levels are examined histologically in each monkey. It is noteworthy—and this needs to be stressed—that by the method described above the inoculum can usually be located in only 1 of these 20 levels; when traumatic paralysis is apparent within 24 hours after inoculation, the inoculum can be located at several levels. Occasionally the inoculum cannot be located, but a root lesion indicative of destruction of neurones somewhere can be found. Occasionally also the inoculum fails to reach the grey matter, and the needle track can be seen in the lateral white matter (Fig. 4); in such cases the absence of clinical manifestations or specific lesions is of no significance in the final evaluation of the test.

In Fig. 2a the damage from the inoculum is minimal, but the needle track can be seen passing through the grey matter of the posterior horn up to the anterior horn. This particular monkey was inoculated with approximately 10^5 TCD_{50} (50% tissue culture infective doses) of the type 1 vaccine (L Sc, 2 ab strain), and no specific lesions are discernible even in the anterior horn cells adjacent to the inoculum, and all the other levels of the lumbar cord from the same monkey were as devoid of specific lesions as that shown in Fig. 2b. In Fig. 3a the inoculation damage involves disintegration

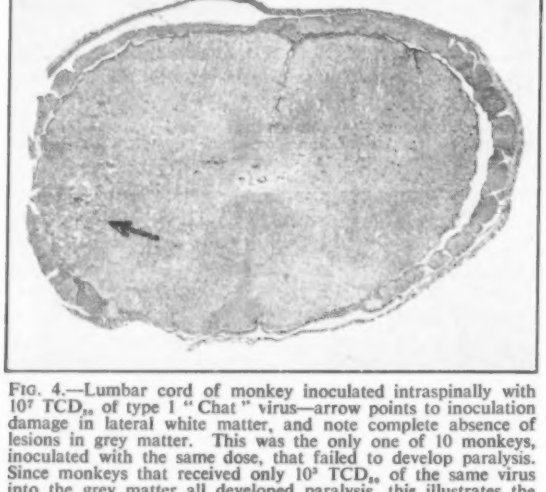


FIG. 4.—Lumbar cord of monkey inoculated intraspinally with 10^7 TCD_{50} of type 1 "Chat" virus—arrow points to inoculation damage in lateral white matter, and note complete absence of lesions in grey matter. This was the only one of 10 monkeys, inoculated with the same dose, that failed to develop paralysis. Since monkeys that received only 10^3 TCD_{50} of the same virus into the grey matter all developed paralysis, this illustrates the innocuity of even large doses of intracerebrally avirulent virus except when it is placed in direct contact with susceptible neurones.

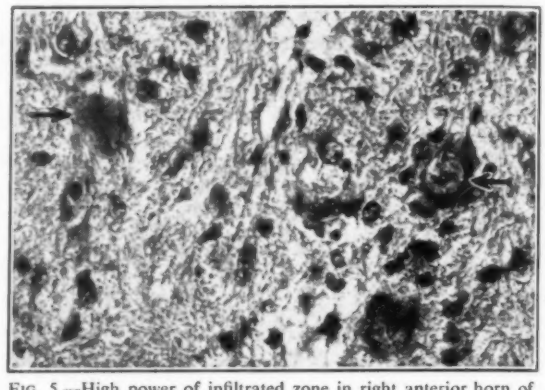


FIG. 5.—High power of infiltrated zone in right anterior horn of Fig. 3a—note intact neurones.

of the grey matter of most of the posterior and anterior horns at this level with slight focal infiltrative lesions on the opposite side. Actually in the midst of the inflammatory reaction in the destroyed anterior horn one can find many shrunken but architecturally intact neurones (see Fig. 5). Despite this evidence of the perfect placement of the inoculum, which in this instance contained about 10^6 TCD_{50} of the same type 1 vaccine, all the other levels of the cord from the same monkey were as devoid of lesions as that shown in Fig. 3b. As previously pointed out, in most instances one can find evidence of either contiguous or scattered focal specific lesions elsewhere in the lumbar cord, and only exceptionally slight focal lesions in the cervical cord, of the monkeys that remain well after spinal inoculation of the three selected vaccine strains.

It is obvious that there is a certain amount of variation in the response of individual monkeys which is not dependent on the accuracy of the placement of the inoculum. Within the limits of these slight variations, however, this method has yielded reproducible

TABLE I.—*Effectiveness and Reproducibility of Described Procedure for Comparing Spinal Neurotropism of Attenuated Polioviruses in Monkeys*

Type 1 Strains							Type 3 Strains			
TCD_{50} Inoculated Log 10	Brunhilde-Enders-Chimpanzee	"Chat" Koprowski (Large Lot)	L Sc, 2 ab (Large Lot)				TCD_{50} Inoculated Log 10	Leon, 12 a_1b (Large Lot)		"Fox" Koprowski (Large Lot)
			Test 1	Test 2 (Rhesus)	Test 3			Test 1	Test 2 (Rhesus)	
					5–8 lb. Monkeys	2·5–4 lb. Monkeys				
7·0–7·2	Not tested	9/10	1?/10	2sl+2?/10	2+3sl/10		6·9	1+1?/10	1*/10	
6·0–6·2	3/4	5/5	1?/5	1+2?/5	3/5	1sl/5	5·9–6·1	0/5		9/10
5·0–5·2	2/3	5/5	1?/5	0/5	0/5	0/5	4·9–5·1	0/5		4/5
4·0–4·2	4/4	3/5				0/4	3·9–4·1			5/5
3·0–3·2	3/4	4/5					2·9–3·1			3/5
2·0–2·2	2/4	Not tested								

Note.—All tests in cynomolgus monkeys of about 5 to 6 lb. (2·2 to 2·7 kg.) except when otherwise indicated. Numerator = number of monkeys showing paralysis of varying extent with onset two days or later after inoculation confirmed by histological evidence of specific poliomyelitic, neuronal lesions of sufficient extent to account for clinical manifestations. Denominator = Number of monkeys inoculated and surviving at least 14 days. Sl = Only limited clinical involvement giving rise to localized weakness or transitory partial paralysis of one leg. ? = Involvement only of toes or localized subsequent extension of traumatic partial paralysis first seen within 24 hours after inoculation, associated with only limited, focal poliomyelitic lesions of insufficient extent to account for clinical manifestations.

* This monkey first exhibited weakness of one foot 17 days after inoculation and progressed to partial paralysis of the leg the next day and no further by the 20th day, when it was sacrificed for study; despite the presence of specific poliomyelitic lesions no virus could be recovered in tissue cultures of various dilutions of an extract of the spinal cord.

Note on Histological Check.—In the few monkeys that failed to show paralysis after inoculation with the "Brunhilde-Enders-Chimpanzee" (excepting one monkey in the $10^{8.2}$ group), "Chat," and "Fox" Koprowski strains, the inoculum was either found in the lateral white matter (Fig. 4) or could not be located in the sections. In the monkeys that failed to show paralysis after inoculation with the "L Sc, 2 ab" and "Leon, 12 a_1b" strains the inoculum, with only few exceptions, was located in the grey matter as shown in Figs. 2 and 3.

results with the same or similar material, in both cynomolgus and rhesus monkeys, as indicated in my previous publications (Sabin, 1956a, 1957a, 1957b) and in Table I. It is obvious from the results obtained with more neurotropic strains such as the Brunhilde-Enders-Chimpanzee (the so-called Brunenders strain used in the British killed-virus vaccine), the "Chat," the "Fox" type 3, and others (Sabin, 1955a), that inocula in the range of 10^2 and 10^3 TCD_{50} can produce paralysis despite the fact that the entire inoculum does not remain at the inoculated site by my procedure of spinal injection. Thus a strain that produces less paralysis at 10^7 TCD_{50} than another at 10^3 TCD_{50} can be regarded as being 10,000 times more attenuated.

I have been led to investigate the effect of certain deviations from this procedure because of differences in results obtained in some studies during the past year. I have previously reported that cultures of virus excreted in the stools of adults and children who were fed the three selected vaccine strains usually showed a definite increase in "spinal" neurotropism (Sabin, 1957b). Verlinde *et al.* (1958), using aliquots of the same large lots of vaccine, found practically no "spinal" neurotropism in tests on cultures of a large number of early and late stools obtained from children who were fed the type 1 and type 2 vaccines. During the past year I again confirmed my original observations in tests on another group of 10 children who received the same type 1 vaccine, and it appeared highly improbable that chance alone was responsible for the difference in our results.

Professor Verlinde informed me that he used a procedure essentially similar to mine except that he put his needle in slowly until he saw cerebrospinal fluid well up, at which time he pushed it in deeper and attached the syringe for inoculation of the virus. In tests on a number of monkeys I found that I could not obtain cerebrospinal fluid when I put the needle in the fourth space above the level of the iliac crests, and could first obtain it only in the third space, which is well below the lumbar enlargement of the spinal cord. I then selected a stool culture of type 1 excreted virus which produced non-progressive paralysis in a dose of $10^{5.4}$ TCD_{50}, and also partly in a dose of $10^{4.4}$ TCD_{50}, and inoculated 12 monkeys intraspinally with the $10^{5.4}$ TCD_{50} in different ways, although in each instance the needle was inserted in a manner to produce a distinct muscular contraction in one limb.

None of the 12 monkeys exhibited any evidence of traumatic paralysis within 24 hours after inoculation. The four monkeys which received this inoculum in the third space, withdrawing the needle somewhat after it hit the ventral body surface of the canal, all remained well; the four monkeys which were inoculated in the fourth space rather close to the ventral bony surface (putting the inoculum almost entirely in the anterior horn) all developed moderate paralysis, three of them only in one leg; of the four monkeys that were also inoculated in the fourth space but with the needle withdrawn about 2 mm. from the ventral bony surface only two exhibited a slight partial, non-progressive paralysis. It seems highly probable, therefore, that the different results obtained by Verlinde *et al.* (1958) may be explained on the basis of placing the inoculum too low in the spinal cord. That Verlinde's method of spinal inoculation can yield positive results with virus of somewhat higher neurotropism is evident from his data on some of the type 3 excreted virus.

A similar explanation probably obtains for the difference in the results that I got in the tests on the large lots of Koprowski's type I (Chat) and type 3 (Fox) vaccine that were used in the Belgian Congo trials (Courtois *et al.*, 1958). In the tests carried out by Koprowski's associates these viruses produced paralysis in only an occasional monkey inoculated intraspinally with the largest doses, while in the tests that I carried out by my standard method the results shown in Table I were obtained. Only 4 of the 55 monkeys used in my tests on the Koprowski strains had some limited traumatic paralysis within 24 hours after inoculation; with few exceptions, the paralysis that developed subsequently was extensive and often involved both lower extremities. Sufficiently extensive specific poliomyelitic lesions to account for these clinical manifestations were found in the lumbar cord, and to a less extent usually also in the cervical cord and medulla. It is obvious from this study that comparisons of neurotropic activity of different strains have significance only with reference to the methods used in the tests.

Dr. J. L. Melnick, using a 27-gauge needle for placing the inoculum in the lumbar enlargement with multiple changes in position during the course of inoculation, obtained a much higher incidence of paralytic manifestations than I did by my method. It is not yet clear whether it is the very thin needle employed in this method or the placement of the inoculum in multiple positions to provide continuous muscular contractions during the period of inoculation, or both, that are important in yielding the more extensive involvement. In at least one test with a 27-gauge needle, Kanda and Melnick (1958) obtained the same results that I did in tests on the type 1 vaccine despite the fact that some of the monkeys received cortisone. A study of the sections of the lumbar cord of monkeys inoculated with the 27-gauge needle and distribution of the inoculum in multiple sites shows that the inoculum is distributed rather widely over many levels of the lumbar cord, and that the retention of most of the inoculum within the spinal cord leads to extensive mechanical disintegration of the grey matter that is associated with a marked inflammatory response.

This method of inoculation is associated with a high incidence of traumatic weakness within 24 hours after inoculation, and the subsequent non-specific inflammatory response and destruction of grey matter can occasionally also lead to further extension of paralysis, for I have seen sections on monkeys with delayed complete paralysis of an extremity in which the non-specific destructive lesions at multiple levels of the cord were obviously responsible for the clinical manifestations. The non-specific destruction of neurones by this method is usually so extensive at multiple levels of the cord that the additional specific viral effect on the contiguous neurones can be sufficient to produce clinical manifestations which would not have occurred as a result of the limited virus activity. Here also, instead of measuring the capacity of the virus to spread to multiple levels of the cord from initially infected cells, the virus is immediately placed at multiple levels of the cord. While this method has obvious advantages for the detection of trace amounts of virus in a killed-virus vaccine, and would also be ideal for testing viruses that are completely devoid of neurotropism in monkeys, it does not appear to be suitable for measuring gradations of activity of strains

that still possess a limited capacity for multiplication and spread from one set of neurones to another.

I have gone to such great length in describing the procedures used in the quantitative estimation of "cerebral" and "spinal" neurotropism, and the factors that must be considered in the interpretation of the results, because it is of the utmost importance for the comparison of results obtained by different investigators as well as for the ultimate standardization and assay of vaccines that may be prepared for human use.

Neurotropism of Viruses Excreted by Vaccinated Individuals and After Multiplication in Contacts

Studies on the neurotropism of virus excreted by individuals after ingestion of attenuated strains of poliovirus have been an integral part of the investigation of every strain, and the results have been reported in a number of previous communications (Sabin, 1955b, 1956a, 1957a, 1957b). It has now been clearly established that when virus cultures, as homogeneous as can be obtained from progeny of single particles by the method of triple-plaque purification, and stable when propagated under specified conditions in monkey kidney tissue cultures, undergo multiplication in the alimentary tract it is possible to show changes in the resulting viral population (Sabin, 1957b). The detection of these changes depends on the use of various selective media. Thus, in testing for virus of increased neurotropism the nervous system of the monkey is the selective medium. If a population of 10 million to 100 million virus particles contains 1,000 particles of greater neurotropism, the nervous system of the monkey can detect their presence, in the same manner as a penicillin-containing medium can detect a small number of penicillin-resistant bacteria among a very large population of penicillin-susceptible organisms—in the first instance it does not mean that the entire viral population has increased neurotropism any more than in the second instance it means that the entire bacterial population is penicillin-resistant.

In the search for virus of increased neurotropism in the stools of vaccinated persons it is important, therefore, on the one hand, to prepare the cultures for monkey inoculation with maximal inocula of virus, and, on the other, to avoid a change in the virus by the method used for cultivation. I have previously reported that the type 2 and type 3 viruses that I selected for incorporation in the vaccine yield 10 to 20 times less virus per cell in cultures with reduced concentrations of bicarbonate than virulent strains, and that even at optimum concentrations of bicarbonate (0.22%) the yield of virus per cell is two to four times higher with the more virulent virus (Sabin 1956a, 1957a). Accordingly it is possible, especially with small inocula of virus, to obtain a viral population in the culture fluid that is not representative of that which existed in the alimentary tract, if the optimum medium is not employed. In my early studies with the plaque-purified type 2 virus excreted in chimpanzee stools, I observed just such an event in which the same stool yielded virus of greatly increased spinal neurotropism when it was grown in monkey kidney cultures which had used up much of their bicarbonate, and no change in neurotropism when it was cultivated in tubes containing fresh medium with a bicarbonate concentration of 0.22%.

Other ingredients in the medium (Li and Jahnes, 1958), including serum (Sabin, unpublished), might also exert a selective influence in favour of virus of increased neurotropism, and for this reason I have used only monkey kidney tissue cultures maintained in serum-free 0.5% lactalbumin hydrolysate, neutralized with NaOH, prior to dilution in Earle's solution containing 0.22% of $NaHCO_3$. It may be noted here that Clarke *et al.* (1958) cultured their stools in a poorly buffered medium containing only about 0.1% of $NaHCO_3$ and 2% calf serum, and that the one stool specimen which yielded virus of specially increased "cerebral" neurotropism (No. 1203—14-day) had only a trace of virus ($10^{2.2}$ TCD_{50}/g.); this means that multiple generations of virus were required in culture with reproduction ultimately occurring at reduced *p*H and concentrations of $NaHCO_3$, circumstances that are especially conducive to the selection of more neurotropic virus. One cannot predict what the results might have been if the same stool specimen had been cultivated under more optimum conditions, but the desirability of repeating such tests can hardly be sufficiently stressed.

One of the important questions in this connexion is whether the human alimentary tract may also preferentially select poliovirus of greater neurotropism. At first glance this might appear to be the case because (*a*) this phenomenon does not occur when the same strains are cultivated in large lots in monkey kidney tissue cultures, and (*b*) such altered virus is more likely to be encountered in the alimentary tract after it has multiplied for many generations, than in the stools obtained during the first few days after ingestion. The available evidence, however, indicates that the appearance of more neurotropic virus in the human alimentary tract is a chance occurrence. If such altered virus had a selective advantage, one would expect it ultimately to replace the original virus that was fed, and this probably occurs when the original virus has a markedly diminished capacity for multiplication in the alimentary tract, as is the case with the mouse-adapted type 2, TN (Dick and Dane, 1957) and the rodent and chick-embryo-adapted MEF_1 (da Silva *et al.*, 1957) strains.

Several years ago I demonstrated that passage of a type 2 virus in mice selected virus particles with a markedly diminished capacity for multiplication in the alimentary tract (Sabin, 1955a). However, the highly attenuated strains that I selected multiply as extensively in the human alimentary tract as do highly neurotropic viruses, as determined by the amount of virus excreted per gramme of stool in comparison with that found in patients with the naturally acquired paralytic disease (Sabin, 1958). I have previously noted (Sabin, 1957a, 1957b) that when multiplication of virus continues over a long period of time in the human intestinal tract, virus of greater neurotropism that was found to be present earlier could not be detected later, and this has also been observed by Verlinde *et al.* (1958) in children who were fed the type 3 vaccine, and by myself in children who ingested the type 2 and type 3 vaccines. When these viruses are grown in large lots in monkey kidney cultures, there are at most only a few generations of viral multiplication, and any mutants that might arise have little opportunity to find cells that have not already been infected by the original virus. The human alimentary tract, however, provides a very large surface, and mutant clones have a better opportunity to find contiguous or distant uninfected cells. The most plausible explanation for the failure of such mutant clones to survive is that they still have to compete with

much larger populations of the original virus possessing a good capacity for multiplication in the intestinal tract.

Furthermore, if the alimentary tract preferentially selected virus of greater neurotropism one would expect that after millions of years of coexistence with man the naturally occurring polioviruses would all be highly neurotropic, and yet actual tests on polioviruses recovered from the stools of healthy children have shown a wide spectrum of neurotropism with many of the wild strains in the attenuated range (Sabin, 1957b). There is indeed reason to suspect that one of the reasons that epidemics come to an end and then often fail to recur for many years in the same community is not dependent merely on depletion of susceptibles, but that the virus changes on continued multiplication in the alimentary tract. This may be one of the reasons that viruses of mixed characteristics and diminished "cerebral" neurotropism can occasionally be recovered from the stools of paralytic patients, but, in a series of tests that I have carried out, rarely if at all from the spinal cord (Sabin, 1956a).

The observation recorded by Dick and Dane (1958), that the virus recovered from the stools of a healthy contact of a paralytic patient yielded the pattern of a mixed population containing attenuated virus on intracerebral inoculation in monkeys, while the stools of the paralysed patient had distinctly more neurotropic virus, may indeed be an example of this phenomenon. It is also quite possible that, in addition to high neurotropism, a poliovirus may have to possess certain other properties, such as a high capacity for multiplication in extraneural tissues other than the alimentary tract, in order for it to be able to invade the nervous system in sufficient concentration to produce clinical manifestations (Sabin, 1956b). It is noteworthy that most of the naturally occurring type 2 and type 3 viruses are as highly neurotropic as the type 1 viruses, and yet almost all epidemics and about 85% of all paralytic cases are caused by the type 1 virus.

I have previously reported that the three strains that I selected for inclusion in the vaccine to be tested on a progressively larger scale in human beings yielded different results in tests for the presence of virus with increased neurotropism in the stools obtained at different times after ingestion (Sabin, 1957b). Although additional studies are still in progress, I should now like to summarize the additional observations that have been made on these strains since the last report in July, 1957. In all of these tests I have concentrated on stool specimens obtained about a week after ingestion, because the maximum amount of virus is usually excreted at that time and accordingly represents the period when virus is most likely to be transmitted to others, and on the last positive stools to obtain a measure of the subsequent appearance of virus with greater neurotropism.

Type 1 Strain (L Sc, 2 ab)

The previous tests (Sabin, 1957b) for "cerebral" neurotropism on 6- to 7-day stool cultures from 20 adult volunteers and 14- to 28-day stool cultures from eight volunteers, indicated a very high degree of attenuation —only 4 out of 120 monkeys inoculated with very large doses of virus exhibited any paralytic manifestations, and at least one of these was clearly the result of a non-cytopathogenic mutant arising in the monkey. The results of intracerebral tests in 40 monkeys on the stool cultures from five triple-negative children, shown in Table II, are of a similar nature, with only three monkeys showing paralytic manifestations—one of them again clearly due to a non-cytopathogenic mutant originating in the monkey. The occurrence of limited, focal neuronal lesions in only 5 of the 37 monkeys that remained clinically well, on the one hand, indicates the "cerebral" innocuity of the recovered virus, and on the other points to the possible presence of at least some virus with an increased capacity for multiplication in the cerebral neurones, for no such lesions have been found in any of the monkeys after intracerebral inoculation of the original virus.

TABLE II.—*Intracerebral Neurotropism of Cultures of Type 1 Poliovirus Excreted by Triple-negative Children at Different Times After Ingestion of Attenuated L Sc, 2 ab Strain*

Name	Age in Years	Days after Ingestion	TCD_{50} Inoculated Log 10	Result	
				Clinical*	Histological†
A. S.	5	7	7·4	0, 0, 0, 0	0, 0, 0, +
		20	7·1	0, 0, 0, 15	0, ++, ++
D. S.	7	7	7·4	0, 0, 0, 0	0, 0, 0, 0
		20	7·4	0, 0, 0, 0	0, 0, 0, 0
S. F.	5	10	6·9	0, 0, 0, 0	0, 0, 0, 0
		21	7·7	0, 0, 0, 0	0, 0, 0, 0
P. F.	9	7	7·1	0, 0, 0, 0	0, 0, 0, 0
		19	7·1	0, 0, 12, 18	0, ±
K. F.	11	5	7·7	0, 0, 0, 0	0, 0, 0, +
		17	7·1	0, 0, 0, 0	0, 0, 0, 0

The indicated dose of virus was administered in a volume of 0·5 ml. into the right thalamic region of cynomolgus monkeys weighing about 6 lb. (2·7 kg.).

* Clinical:—15 = Monkey exhibited partial paralysis of lower extremities 15 days after inoculation. 0 = No paralysis observed. 18 = Weakness of right upper extremity 18 days after inoculation, which by 21 days progressed to partial paralysis; *no cytopathogenic virus was found* in the spinal cord (various dilutions tested to avoid zone), but focal poliomyelitis lesions limited to one side of the cervical and upper thoracic cord were present.

† Histological examination involved 60 to 80 levels of spinal cord of the clinically negative monkeys. 0 = No poliomyelitis lesions. ± = One old, focal neuronal lesion involving only one level of 84 examined. + = Focal lesions in many levels but little or no loss of neurones. ++ = More extensive than + but many levels entirely negative.

The tests for "spinal" neurotropism on the virus in late stools from eight adult volunteers all showed some increased activity. Although the spinal titrations have not yet been completed on all the stool cultures from the five triple-negative children, a distinct increase in paralytogenic activity even with doses in the range of 10^4 TCD_{50} and less were found in at least three. Studies now in progress on 10 additional children also show an increase in "spinal" neurotropism. I was unsuccessful in obtaining spread of the type 1 virus in one institutional study where about 90% of the children were naturally immune to this type and therefore had no stools of contacts to study. Material on contacts made available by Drs. John Fox and Henry Gelfand from their family studies in New Orleans is now under investigation.

Verlinde *et al.* (1958) tested for "spinal" neurotropism 19 stool cultures from 12 children and one adult, who received an aliquot of the same large lot of the type 1 vaccine; these included seven cultures of stools obtained 14 to 21 days after ingestion. Each culture was inoculated undiluted and diluted 1:10 into each of two cynomolgus monkeys, and the incidence of paralytic manifestations was less than I obtained with the original virus (Table I). Among 58 monkeys inoculated with 10^6 to $10^{8.5}$ TCD_{50}, only 4 exhibited any paralytic manifestations, and among 18 monkeys inoculated with $10^{4.8}$ to $10^{5.8}$ TCD_{50}, none was paralysed. They also obtained no evidence of paralysis in 10 monkeys inoculated with five original stool suspensions in doses of 10^2 to $10^{4.3}$ TCD_{50}. In my

preceding discussion on methods of inoculation I proposed a possible explanation for the difference in the results obtained by Verlinde and myself. Although the data of Verlinde *et al.* (1958) cannot be used as a measure of increase in neurotropism of excreted virus, they nevertheless show that the viruses they recovered were distinctly attenuated.

Smorodintsev *et al.* (1958) reported a most interesting series of studies on children who were fed type 1 virus prepared from the terminal dilution purified L Sc strain that I supplied them. This is the strain that I found to be inhomogeneous upon examination of the progeny from different plaques (Sabin, 1956a), and from which I selected the optimum L Sc, 2 ab triply purified plaques for the type 1 vaccine. Smorodintsev *et al.* carried out their studies in institutions in which 95% of the children were triple-negative, and observed extensive spread of this virus. While they observed a slight increase in neurotropism of the excreted virus, it was no greater after an estimated four to five natural human passages than it was in the stools of the children who received the original culture fluid. They, furthermore, carried out eight serial passages of the virus in children—the stools of several children obtained two to four weeks after feeding were cultured in monkey kidney, tested in monkeys, and then fed to another group of triple-negative children for eight consecutive passages — without observing any increase in neurotropism beyond that found in the stools excreted by the children who received the original culture fluid.

Horstmann *et al.* (1957a), working with an aliquot of the terminal dilution purified L Sc strain that I supplied to them, reported that tests in monkeys on the last positive stool specimens representing first and second human passage materials "showed very slight increases in virulence" in only two of nine specimens tested.

Type 2 Strain (P 712, Ch, 2 ab)

The previous tests (Sabin, 1957b) for "cerebral" neurotropism on 5- to 10-day stool cultures from 12 adult volunters and 21- to 61-day stool cultures from five volunteers, indicated a high degree of attenuation—only 5 out of 81 monkeys inoculated with very large doses exhibiting any paralytic manifestations, all five occurring with the 7- and 21-day stools of one of the 12 volunteers. The results of intracerebral tests in 66 monkeys on 12 7- to 56-day stool cultures obtained from the same group of five triple-negative children that were fed the type 1 and type 3 vaccines prior to receiving the type 2 virus are of a similar nature (Table III).

In this study the initial screening tests were purposely carried out with a 1-ml. inoculum, and it is noteworthy that in each instance in which some of the monkeys exhibited paralysis (A. S., 36-day; P. F., 36-day; K. F., 10-day) and the test was repeated, giving the same dose of virus in a 0.5-ml. inoculum, no paralysis was observed. It is also noteworthy that in three of the paralysed monkeys tissue-culture tests on the spinal cord yielded a zone phenomenon indicating the presence of both non-cytopathogenic and cytopathogenic virus, and in one paralysed monkey no cytopathogenic virus was found in any dilution of the spinal cord despite the presence of typical polio lesions—findings indicative of the effects of mutants arising within the nervous system of the monkeys. Another finding of interest is that in the instances in which some paralytic monkeys were found in the tests on the 36-day stools (A. S. and P. F.) no paralysis was found in any of the monkeys inoculated with the 55- or 56-day stools from the same children. This failure of more neurotropic virus to accumulate or persist in the alimentary tract was confirmed by tests for "spinal" neurotropism on the same specimens.

TABLE III.—*Intracerebral Neurotropism of Cultures of Type 2 Poliovirus Excreted by Initially Triple-negative Children at Different Times After Ingestion of Attenuated P 712, Ch, 2 ab Strain Administered After Previous Feedings of Types 1 and 3 Viruses*

Name	Days after Ingestion	Result after Inoculation of Indicated Amounts (Log 10)							
		Dose	Paral.	Dose	Paral.	Dose	Paral.	Dose	Paral.
A. S.	7	8·4	0, 0	6·4	0, 0				
	36	8·0	0, 0	6·0	0, 13				
					0, 0	5·0	0, 0		
	56	7·2	0, 0	5·5	0, 0	4·5	0, 0		
D. S.	9	7·7	0, 0	5·7	0, 0				
	35	8·2	0, 0	6·2	0, 0				
S. F.	8	7·6	0, 0	5·6	0, 0				
	35	7·7	0, 12*	5·7	0, 0				
P. F.	10			6·7	0, 0	4·7	0, 0		
	36	8·2	0, 8	6·2	0, 12*				
					0, 0	5·2	0, 0		
	55	7·1	0, 0	5·4	0, 0	4·4	0, 0		
K. F.	10	8·0	0, 0	6·0	17*, 17†				
					0, 0	5·0	0, 0	4·0	0, 0
	20	8·4	0, 13 tr.	6·4	0, 0				

The initial inoculations of the undiluted and 10^{-2} dilutions of the culture fluids (except the 55- and 56-day specimens) were all in a volume of 1 ml. given entirely into the right thalamic region. In the repeat tests the same dose of virus was given in a volume of 0·5 ml.; the results for 1 ml. are given in the numerator and those for 0·5 ml. in the denominator when the same dose was given in different volumes.

tr = Paralysis slight and transitory.

* Zone phenomenon in test for virus in spinal cord, indicating presence of both non-cytopathogenic and cytopathogenic virus.

† No cytopathogenic virus found in any dilution of spinal cord suspension.

The previous tests for "spinal" neurotropism showed a definite increase in the "late" stools of at least two of the four volunteers tested, and the tests on the stools of the five children showed a similar, sometimes transitory, increase in four. Here again it is noteworthy that Verlinde *et al.* (1958), who tested 11 stool cultures from seven children after ingestion of an aliquot from the same type 2 vaccine, found no evidence of "spinal" neurotropism. Their tests included cultures on five stools obtained 13 to 23 days after ingestion; only one of 26 monkeys receiving 10^6 to $10^{7.7}$ TCD_{50} of virus exhibited paralysis (the one positive monkey received 25 million TCD_{50}), and none of 12 inoculated with 10^5 to $10^{5.8}$ TCD_{50}, and none of six inoculated with $10^{4.3}$ to $10^{4.5}$ TCD_{50}. Again, while their results cannot be used as a measure of increase in neurotropism, because of the method they used, they nevertheless point to the attenuated characteristics of the excreted virus.

Smorodintsev *et al.* (1958) carried out studies with type 2 virus similar to those described for type 1. The virus they used was prepared from the "P 712, 10 ab_1" strain that I sent them. This is the triply purified plaque progeny from which I selected the P 712, Ch, 2 ab strain used for preparation of the type 2 vaccine (Sabin, 1956a, 1957a, 1957b). In my preliminary tests with the P 712, 10 ab_1 strain in chimpanzees, I found that some excreted virus of increased "spinal" neurotropism and one did not. I therefore used the stool culture of the one chimpanzee which yielded negative results on spinal inoculation, for

further analysis of single-plaque progeny and selected the P 712, Ch, 2 ab progeny, but there is probably no difference between it and the P 712, 10 ab_1 strain. Smorodintsev *et al.* (1958) found no evidence of greater neurotropism of the virus in the stools of contacts than in those who received the original culture fluid. Furthermore, during the course of five experimental consecutive passages in triple-negative children they observed a partial increase in both "cerebral" and "spinal" neurotropism in the stools of the fourth human passage, which was no longer found in the stools of those who received it for the fifth human passage.

Type 3 Strain (Leon 12 a,b)

The previous tests (Sabin, 1957b) for "cerebral" neurotropism on 11 6- to 7-day and on 11 20- to 61-day stool cultures from adult volunteers in 137 monkeys indicated a greater increase in neurotropism of the virus in the stools of 2 of the 12 volunteers studied than was observed with the type 1 and type 2 viruses. Here, also, there was evidence that the paralysis in a few monkeys was associated with mutants arising in the nervous system of the monkeys, because no cytopathogenic virus could be recovered from the spinal cord. The results of intracerebral tests in 99 monkeys on 11 stool cultures and five original stools obtained 6 to 21 days from the same group of five triple-negative children who received the type 3 vaccine 21 days after the type 1 are shown in Table IV. Here also the initial screening tests were purposely carried out with a 1-ml. inoculum, and in several instances different results were obtained when the same dose was inoculated in 0.5 ml. The greater "cerebral" neurotropism is also evident in these tests, but it is noteworthy that in all instances the results are indicative of a mixed population of virus particles in that some monkeys inoculated with larger amounts failed to develop paralysis while others receiving smaller amounts did. Paralysis also appeared in 3 of the 19 monkeys inoculated with the original stools, but the zone phenomena found in the tissue-culture tests on the spinal cords of two and the prolonged incubation period in the third suggest the possibility that the paralysis may have resulted from mutants arising during the course of multiplication of the virus in the nervous system of the monkeys. It is again noteworthy that in child S. F., the 20-day stool cultures gave completely negative results (with 1-ml. inocula) while the 6-day and 13-day stools obviously contained some virus of greater neurotropism.

During the course of a recent study in association with Krugman, Giles, Barnes, and Wang (unpublished), in which the type 3 vaccine was fed to children who had previously had four doses of Salk vaccine, stools were also collected from a number of contacts who lived with them in the same institution under conditions particularly conducive to faecal spread. Serological tests on these children over a period of 15 months prior to administration of the oral vaccine gave no indication of spontaneous infection with polioviruses, although there was ample evidence that other enteroviruses of one kind or another were in almost constant circulation. Type 3 poliovirus appeared in three of six contacts whose stools were examined at frequent intervals. The time of appearance of the virus in their stools shown in Table V suggests that at least one of the children may have acquired his infection after more than one passage in the intestinal tract of the others. The results of the preliminary tests for cerebral neurotropism with 1-ml. inocula show the attenuated characteristics of the virus that has multiplied for many additional generations in their intestinal tracts.

In another unit of this institution a type 1 test was in progress at the same time. These children had no direct contact with those who received the type 3 vaccine, but about six weeks after the beginning of the test type 3 virus was isolated from eight children whose stools were being tested at frequent intervals. The only indirect contact between the two units may have occurred through the medium of night attendants who administered intramuscular injections of medication in the buttocks. Although no virus carriers were found among the five attendants four weeks after the first appearance of the type 3 virus in the second unit, the possibility, nevertheless, exists that they may have introduced it, although it is also possible that a "wild" type 3 virus was introduced from outside. The preliminary tests on the stool cultures of these children, shown in Table V, show that the virus was of an attenuated character.

TABLE IV.—*Intracerebral Neurotropism of Some Original Stool Suspensions and Stool Cultures of Type 3 Poliovirus Excreted by Triple-negative Children at Different Times after Ingestion of Leon 12 a_1b Strain Administered after Previous Feeding of Type 1 Virus*

Name	Days after Ingestion	Stool Cultures—Dose Log 10								Original Stool	
		Dose	Paral.	Dose	Paral.	Dose	Paral.	Dose	Paral.	Dose	Paral.
A. S.	15	8·4	0, 5	6·4	0, 0						
	21			6·7	0, 0			4·7	0, 0		
D. S.	9	8·2	9, 9	6·2	6, 13 tr. 0, 10						
	21	7·4	9, 13			5·2 5·4	13*, 14 8, 13 0, 0	4·2 4·4	0, 16 0, 12*	3·2 3·4 2·4	0, 12 0, 0 0, 0
										3·4	0, 0, 16*
										2·4	0, 0, 0, 12*
S. F.	6	8·2	0, 15	6·2	0, 11 0, 16						
	13	7·4	slight 17, 0			5·2 5·7	0, 0 10, 15	4·2 4·7	0, 0 0, 0	3·7	9, 16
	20	7·4	0, 0			5·4	0, 0				
										4·4	0, 0, 0, 24
										4·9	0, 0, 0, 0
P. F.	6	8·7	0, 0	6·7	0, 16 0, 0	5·7	0, 25	4·7	0, 0		
	14	8·7	10, 13 tr.	6·7	0, 0						
K. F.	6	8·4	0, 12	6·4	0, 0						
	20	7·4	17, 20 tr. tr.			5·4	0, 20* 0, 13	4·4	0, 22	4·0	0, 0, 0, 0

See notes at foot of Table III.

Verlinde *et al.* (1958) tested 24 stool cultures obtained from 14 children 4 to 44 days after ingestion of aliquots of the same large lot of type 3 vaccine that I used in my studies. These cultures, 14 of them representing 15- to 44-day stools from nine children, were tested intraspinally in 96 cynomolgus monkeys and intracerebrally in 22 monkeys. Seventeen specimens from 12 children yielded negative results—only 2 out of 54 monkeys inoculated intraspinally with 1 million to 100 million TCD_{50} exhibiting any paralysis. In two children there was definite evidence of a transitory presence of more neurotropic virus by both the spinal and the intracerebral methods of testing: by the latter method, only the monkeys inoculated with amounts in excess of 1 million TCD_{50} exhibited paralysis. In both children the last stool specimens, in one instance obtained 21 days and in the other 33 days after ingestion, gave completely negative results in the monkeys that received large doses of virus by their method of spinal inoculation. Although the methods of testing were different, it is nevertheless evident that in all instances the excreted viruses were of an attenuated character.

Clarke *et al.* (1958) reported intracerebral tests in monkeys on 10 stool cultures obtained from five children 1 to 31 days after feeding an aliquot of the same large lot of type 3 vaccine. It has already been pointed out that the highly traumatic technique of intracerebral inoculation that they used (0.5 ml. into each thalamic region) is not suitable for an accurate measure of "cerebral" neurotropism, and that the culture medium they used for enriching the amount of virus in the stools was conducive to increasing the proportion of more neurotropic virus that might have been present there. Nevertheless, the results that they reported were (with one possible exception) not significantly different from those I had previously reported as indicating that a variable proportion of the virus excreted after ingestion of the type 3 vaccine is more neurotropic than that which was fed. Some of the monkeys that they recorded as paralytic, particularly those with relatively short incubation periods after inoculation of about 10 million to 140 million TCD_{50} of virus, may represent animals in which the virus invaded the spinal cord *directly* as a result of the traumatic inoculation, while others were apparently recorded as paralytic when the cause of their paralysis was not the poliovirus found in the spinal cord.

Thus, according to a personal communication from Dr. Goffe, a monkey recorded as having its onset of paralysis six days after inoculation of 890,000 TCD_{50} of the 7-day stool culture of case 1201, actually died of bacterial meningitis and exhibited only minimal polio lesions. It has already been pointed out that rather extensive specific poliomyelitic lesions can be found in monkeys without any clinical evidence of paralysis, and only the loss of a great many neurones in multiple levels of the cervical or lumbar cord constitutes histological confirmation that paresis or ill-defined paralysis, especially when it is not clearly flaccid, has been caused by the action of poliovirus. There is also evidence that paralysis in some of their monkeys was associated with non-cytopathogenic mutants which must have arisen in the nervous system of the monkeys, for in their cases 1205 and 1308 they failed to recover virus in tissue culture from three of the five monkeys recorded as being paralytic.

Dr. Goffe also wrote me that, in 5 of the 16 cords from which virus was recovered, a cytopathogenic effect was demonstrable only in the second passage, suggesting that the original material probably contained interfering non-cytopathogenic virus. The virus excreted by four of the five children was of a distinctly attenuated character, and only the 14-day stool culture of case 1203 yielded results comparable to those I found in child D. S. (Table IV). The need for repeating the tests on

TABLE V.—*Preliminary Tests for Intracerebral Neurotropism of Type 3 Virus Grown from Stools of Children Having Direct or Indirect "Contact" with Children who were Fed Type 3 Vaccine*

Type of Contact	Name	Days after Feeding Vaccine to Others Stools of Contacts were:			TCD_{50} Inoculated Log 10	Clinical Result
		Negative for Type 3 Virus	Positive for Type 3 Virus	Used for Monkey Test		
Direct 2 or more human passages of virus	Hel.	0, 2, 4, 10, 27, 41, 52, 59	6, 14, 20	20	7·7 5·7	0, 0 21*
	Hir.	0, 2, 4, 6, 9, 20, 27, 41, 50, 55	13	13	8·5 6·5	0, 0 0, 0
	Fis.	0, 2, 4, 6, 9, 20, 28, 52, 55	42	42	7·7 5·7	0, 14 0, 18
Indirect 3 or more human passages of virus or Introduction of "wild" virus into unit	Bos.	0, 2, 4, 6, 9, 13, 20, 28, 52, 55	41	41	8·2 6·2	0, 7 0
	Dil.	0, 2, 4, 6, 9, 13, 20, 27, 50, 55	41	41	7·4 5·4	7, 10 0, 8 transit
	Ros.	0, 3, 5, 6, 10, 11, 14, 20, 27, 55	41, 50	41	7·2 5·2	6, 7 0, 7
	Sch.	0, 2, 4, 6, 10, 13, 21, 27, 55	41, 50	50	7·9 5·9	4, 5 0, 16
	Hau.	0, 2, 4, 6, 9, 13, 20, 27, 56	41, 51	51	7·2 5·2	0, 17 0, 0
	Kee.	0, 2, 4, 6, 9, 13, 20, 27	41, 50, 55	55	6·9 4·9	0, 9 0, 13
	Ort.	0, 2, 4, 6, 9, 13, 20, 27	41, 50, 55	55	7·4 5·4	0, 12 transit 0, 21†
	Lev.	0, 3, 5, 7, 10, 14, 28, 42, 49	50	50	7·2 5·2	6, 8 0, ?

* Only trace of cytopathogenic virus recovered after long delay despite presence of acute polio lesions in spinal cord.
† Marked zone phenomenon in tissue culture indicative of presence of non-cytopathogenic interfering virus in spinal cord.
Note.—All monkeys in this test were inoculated with 1 ml. into right thalamic region.

such stool specimens with cultures containing optimum medium, to obtain a better estimate of the characteristics of the virus present in the original stool, were discussed earlier.

Smorodintsev *et al.* (1958) carried out studies with the type 3 virus similar to those described for the types 1 and 2 viruses, and obtained similar results. The virus they used was prepared from the triply purified, Leon 14 ab, plaque progeny that I sent them. The Leon 12 a_1b plaque progeny, which I finally selected for inclusion in the vaccine, and the Leon 14 ab plaque progeny, were both derived from the same attenuated, terminal-dilution-purified "Leon" virus (Sabin, 1956a, 1957a, 1957b), and were the only plaque progeny which on repeated tests failed to produce paralysis in any of the monkeys inoculated intraspinally (by the method I described) with the largest doses of virus. In preliminary feeding tests in chimpanzees, virus of increased neurotropism was excreted by those receiving the 14 ab strain but not by those receiving the 12 a_1b strain (Sabin, 1957b), and that was the reason why I selected the Leon 12 a_1b strain for the type 3 vaccine. Smorodintsev *et al.* (1958) reported that highly attenuated virus was excreted by the contacts as well as by the children who received the original culture fluid. Furthermore, during the course of six experimental consecutive passages in triple-negative children, they found that a partial increase in both "cerebral" and "spinal" neurotropism, which was observed in the stool cultures of the fifth human passage, was not evident in the sixth passage.

Other Methods for Testing Variations in Characteristics of Excreted Virus

On the basis of all information available to me there is thus far no *in vitro* method that can be substituted for monkeys in measuring the *degree* of neurotropism of a poliovirus. I have previously pointed out that the type 2 and type 3, but not type 1, highly attenuated strains produced much smaller plaques under agar overlays with full (0.22%) concentrations of $NaHCO_3$ than their highly neurotropic parents (Sabin, 1957a), but I found that the highly attenuated type 3 Leon 12 a_1b virus, which showed no increase in neurotropism after two weeks of multiplication in the posterior pharyngeal wall of chimpanzees, nevertheless produced distinctly larger plaques than the virus that was fed.

The capacity to produce plaques under agar overlays containing a reduced (0.05%) concentration of $NaHCO_3$ (the so-called "d" character) has been found lacking in all highly attenuated strains (Vogt *et al.*, 1957), but I have already reported that the progeny of four plaques, especially selected by Dulbecco and Vogt from the Leon 12 a_1b and Leon 14 ab triple-plaque purified strains by picking late mutants on cultures with "acid" agar overlays, exhibited no change in spinal neurotropism for monkeys, although they possessed a 100 to 1,000 times greater capacity for producing plaques under "acid" overlay (Sabin, 1957a).

Hsiung and Melnick (1958), in a comprehensive study on the relation of the "d" character to neurotropism in naturally occurring and experimentally attenuated strains of poliovirus, as well as in polioviruses excreted after the feeding of attenuated strains, found no evidence of marked "cerebral" neurotropism in many "d+" strains exhibiting a high efficiency of plaque formation under overlays with reduced concentrations of $NaHCO_3$. They also quoted unpublished studies of Horstmann and Maas, which indicated (*a*) that misleading information regarding the "d" character of poliovirus in stools may be obtained if the specimen is cultured in a low-bicarbonate instead of a high-bicarbonate medium; and (*b*) that virus exhibiting a high efficiency of plaque formation under low-bicarbonate agar overlay (d+ character) can be distinctly attenuated when tested for neurotropism in monkeys.

Recently Kanda and Melnick (1958) reported that neurotropically virulent and attenuated polioviruses grew differently on primary monkey-kidney tissue cultures and on a stable line of monkey-kidney cells (the "MS" line)—the attenuated strains yielding 1/10,000 the amount of virus and distinctly smaller plaques in the "MS" cells. A total of 110 stool and stool-culture specimens from 40 volunteers obtained at different times after ingestion of portions of the large lots of the type 1, 2, or 3 vaccine, which I had previously tested for neurotropism (Sabin, 1957b), were tested in Dr. Melnick's laboratory for the so-called "MS" character—that is, the capacity to grow equally well on the "MS" line of cells as on primary monkey-kidney cells, a property possessed by the virulent polioviruses.

It is noteworthy that the virus present in 18 original stool extracts and in 18 stool cultures from 10 volunteers, obtained 7 to 61 days after ingestion of the type 3 vaccine, and in 13 original stool extracts and in 16 stool cultures from 10 volunteers, obtained 7 to 61 days after ingestion of the type 2 vaccine, in all instances lacked the "MS" character of the virulent polioviruses, despite the fact that the monkey tests on the same specimens showed a distinct increase in neurotropism in at least one of the type 2 volunteers and two of the type 3 volunteers. The tests on 19 original stool extracts, obtained from as many volunteers six to seven days after ingestion of the type 1 vaccine, indicated a partial "MS" character in six, which in five instances was not detected in the cultures prepared from them. The 28-day culture from the one volunteer, whose seven-day original stool and stool culture were "MS" positive, as well as 24 other stool cultures, obtained from 19 other volunteers 6 to 28 days after ingestion of the type 1 vaccine, all were "MS"-negative—that is, possessed the characteristics of the neurotropically attenuated polioviruses. The one "MS"-positive stool culture had no greater "spinal" neurotropism in monkeys than the "MS"-negative stool cultures.

Persistence of Antibody and Resistance of the Alimentary Tract to Infection

I have previously reported that the antibody response resulting from multiplication of attenuated polioviruses in the alimentary tract varies with the individual, the age of the person, and the strain and type of virus fed (Sabin, 1956a, 1958). Accordingly, observations based on a single strain, particularly one that has a limited initial capacity for multiplication in the human alimentary tract, cannot properly be used for generalizations about the effects of attenuated polioviruses (Dick and Dane, 1958; Dane *et al.*, 1958). Furthermore, the statement occasionally encountered in the literature, that natural infection results in the development of neutralizing antibodies of high titre

which persist without significant change in level, is now known to be incorrect.

The recent studies of Lennette and Schmidt (1957) on patients with clinical poliomyelitis have shown that some respond with high titres and others with low, and that in most individuals the titre drops from fourfold to twentyfold during the course of a year or two following infection. Le Bouvier (1957), in a study of antibody levels in persons of different age in different population groups, also obtained evidence of a decline in levels over the years, even in unsanitary areas where polioviruses are extensively disseminated, suggesting that reinfection with the consequent boost in the level of antibody does not occur in such populations after a certain period of years. In my studies on adult human volunteers I have repeatedly encountered individuals with minimal or no demonstrable neutralizing antibodies for one or more types of poliovirus who exhibited complete resistance to infection of the alimentary tract with large doses of attenuated poliovirus—that is, the virus not only failed to multiply but there was also no antibody response (Sabin, 1956a, 1957b, 1958).

TABLE VI.—*Persistence of Type 1 Antibody Resulting from Feeding Various Attenuated Type 1 Polioviruses Correlated With Resistance of Intestinal Tract to Subsequent Feeding of About 10^6 TCD_{50} of Virus**

Strain Originally Fed	Name	Interval after Feeding (Months)	Antibody			Resistance of Intestinal Tract at Indicated Time
			*p*H	Cytopathogenic		
				2-Day	8-Day	
L Sc, 2 ab	A. S.	3	2,048	3,200	3,200	
		9		3,200	3,200	
	D. S.	3	2,048	640	640	
		9		2,000	320	
L Sc ..	Moo.	3	8	16	16; 4	
		16	8	16	6	Complete*
(Terminal dilution progeny)	Ree.	3	48	64	48; 20	,,
		16	32	48	12	
	And.	3	64	12	0	
		9	48	4	0	,,
	Joh.	2	12	16	4	
		9	24	16	4	,,
	Klo.	3	192	320	32	
		9	128	320	32	,,
	Smi.	3	128	200	32	
		9	64	32	32	Partial†
"P 2149"	Col.	3	384	320	320	
		16	1,024	640	320	Complete
	Cou.	3	384	640	320	
		16	384	640	320	,,
"P 2226"	Dam.	3	512	640	320	
		16	256	320	320	,,
	Dil.	3	128	256	180; 32	
		16	96	256	48	,,
Mahoney KP 33	Hac.	3		2,000	640	
		12			2,000	
		30			3,200	
	Har.	3			320	
		12			320	
	Mal.	3			32	
		12			32	
	Tro.	3			4	
		12			20‡	
	Ric.	3			32	
		12			32	
	Car.	3			32	
		6			32	
	Wal.	3			32	
		6			32	

* The challenge virus was the L Sc, 2 ab strain; and five controls, without homotypic antibody, who were fed the same dose at the same time all developed intestinal infection. Complete resistance = No virus detected in stools between 5 and 28 days after ingestion and no rise in antibody.

† Partial resistance = Virus found in stools for first 14 days in smaller than usual amounts associated with distinct rise in antibody. Unlike the other volunteers this man exhibited early interference followed by limited viral multiplication for a period of seven days after the first feeding nine months earlier.

‡ This man received type 2 virus at three months, which was followed by a boost in his type 1 antibody.

Note.—Only A. S. and D. S. are children. The others were all young adults, living away from children, in an environment where no spontaneous spread of polioviruses was detected.

TABLE VII.—*Persistence of Type 2 Antibody Resulting from Feeding Various Attenuated Type 2 Polioviruses Correlated With Resistance of Intestinal Tract to Subsequent Feeding of About $10^{5.7}$ TCD_{50} of Virus**

Strain Originally Fed	Name	Interval after Feeding (Months)	Antibody			Resistance of Intestinal Tract at Indicated Time
			*p*H	Cytopathogenic		
				2-Day	8-Day	
P 712, Ch, 2 ab	A. S.	1·25	256	320	200	
		8		320	32	
	D. S.	1·25	512	320	320	
		8		320	32	
P 712	Wal.	3	768	320	32	
		8	512	320	200	Complete
(Terminal dilution progeny)	Wai.	3	512	32	32	
		8	512	32	32	,,
	Boy.	3	768	320	320	
		9	1,024	320	64	,,
	Bes.	3	768	200	32	
		15	1,024	200	64	,,
	Die.	3	768	320	200	
		15	768	200	32	,,
	Tru.	3	2,048	2,000	200	
		15	1,536	320	64	,,
	Wat.	3	1,024	320	200	
		15	1,024	200	64	Partial†
YSK	Pee.	3			200	
		7			320	
KP 51		13			320	
	Dou.	3			200	
		6			200	
	Ros.	3			32	
		6			64	
	Nic.	3			32	
		6			320+‡	

* The challenge virus was the P 712, Ch, 2 ab strain; and five controls, without homotypic antibody, who were fed the same dose at the same time all exhibited intestinal infection.

† Partial resistance = Small amounts of virus detected in stools for period of 10 days associated with rise in antibody. It is noteworthy that, unlike the other volunteers, this man was originally fed a mixture of types 1 and 2 polioviruses, and both multiplied simultaneously.

‡ This man received type 3 virus at three months, which was followed by a boost in his type 2 antibody.

The data shown in Tables VI, VII, and VIII summarize the results on persistence of antibody in 19 individuals who had been fed various type 1 strains, 13 individuals fed various type 2 strains, and 10 individuals fed the attenuated type 3 "Leon" virus. The data on tests for resistance of the alimentary tract to reinfection, in relation to the level of antibody at the time of the test, are also shown for 24 of these individuals. The results are given separately for the combined low-avidity and high-avidity antibody, as determined by the *p*H method and partly also by early (two-day) readings in the cytopathogenic method, and for high-avidity antibody represented by the eight-day reading in the cytopathogenic test (using serum-virus mixtures that are incubated only one hour at room temperature and subsequently undergo a 1:11 dilution in the culture fluid of the tubes used for the test). The titres are the 50% end-points calculated for 0.2 ml. of the original serum; the dilution which the serum-virus mixture undergoes following addition to the test system is not involved in this calculation. With few exceptions, the comparative tests for level of antibody at different times were carried out simultaneously with sera that had been preserved in the frozen state.

While there are certain variations in the levels of high-avidity and low-avidity antibody during the first three months after infection, when the antibody changes in its qualitative characteristics (see Table IX), it is evident that the level of antibody present at three months had undergone little or no significant change in titre during the subsequent periods, varying from 6 to 16 months after feeding, except for the rises in the few individuals who were fed other types of poliovirus in the interim. In the type 2 group (Table VII) the

high-avidity titre showed a drop of threefold to tenfold in six instances, while the low-avidity antibody titre remained unchanged. It is particularly noteworthy that the persistence of antibody was not dependent on the titre—the low levels persisted as well as the high ones. Of special interest is the fact that resistance of the alimentary tract was in no way related to the level of antibody, and in three instances complete or marked resistance was present in individuals without high-avidity antibody and only minimal levels of low-avidity antibody. It must be remembered that on primary exposure to the virus there was multiplication in the alimentary tract of all of these individuals. These data, taken together with the demonstration that a certain proportion of adults without demonstrable antibody by the usual methods have been found to have resistant alimentary tracts, indicate that the persistent resistance of the alimentary tract to infection with poliovirus is not dependent on persistence of antibody.

TABLE VIII.—*Persistence of Type 3 Antibody Resulting from Feeding Attenuated Type 3 Poliovirus Correlated with Resistance of Intestinal Tract to Subsequent Feeding of About $10^{5.9}$ TCD_{50} of Same Strain**

Strain Originally Fed	Name	Interval after Feeding (Months)	Antibody			Resistance of Intestinal Tract at Indicated Time
			*p*H	Cytopathogenic		
				2-Day	8-Day	
Leon 12 a_1b	A. S.	2	128	64	50	
		8·5	48	48	16	
	D. S.	2	64	64	12	
		8·5	32	24	24	
Leon	Bye.	3	64	32	6	
		9	32	32	32	Complete
(Terminal dilution progeny)	How.	3	256	320	200	
		9	256	320	200	,,
	Tod.	3	256	320	64	
		9	128	200	32	,,
	Per.	3	128	64	32	
		8·5	128	32	32	,,
	Tom.	3	128	32	3	
		8·5	128	64	3	,,
	Qui.	3	16	8?	4	
		8·5	8	4?	0	Marked†
	Sul.	1	16		20	
		2	16		3	
		3	16		0?	Complete
		6			2	
		12			0?	
	Rod.	3			4	
		6			32‡	
		9			32	

* The challenge virus was the Leon 12 a_1b strain; and 13 controls, without homotypic antibody, who were fed the same dose at the same time all exhibited intestinal infection.

† Marked resistance=Only a trace of virus was detected once in the stools on the 14th day after feeding, and this was associated with a marked rise in antibody.

‡ This man received type 2 virus at three months, which was followed by a boost in his type 3 antibody.

Recent studies in association with Dr. Giacomo Messore on large numbers of stools from known susceptible and immune children and adults, prior and subsequent to infection with orally administered attenuated polioviruses, showed that resistance of the alimentary tract is not associated with the presence of any specific antibody or other neutralizing principle in the faeces. The high susceptibility of the intestinal tract in the presence of high levels of neutralizing antibody in the blood resulting from killed-virus vaccine, and the high resistance of the intestinal tract in the absence of readily demonstrable antibody in the blood or faeces, strongly suggest that the resistance is based on specific cellular rather than humoral factors. It also follows from this that intestinal infections that are originally limited in extent by virtue of dose, simultaneous infection with more than one type, interference by other enteric viruses, or inadequate multiplication of an experimentally attenuated virus, may result in only partial resistance without reference to demonstrable antibody—and this is borne out by some of the data in Tables VI, VII, and VIII, as well as by observations on human beings with naturally acquired antibody (Sabin, 1957b; Fox *et al.*, 1957; Horstmann *et al.*, 1957a).

TABLE IX.—*Low-avidity and High-avidity Neutralizing Antibody in Young Adults Following Ingestion of only One Type of Vaccine. Variation in Relation to Type of Virus Ingested, Dose, Extent, and Duration of Excretion of Poliovirus in Stools*

Type of Vaccine	Dose	Name	Excretion of Virus		Antibody Response at Indicated No. of Days							
			Duration Days	Peak Titre TCD_{50} g. Log 10	Low+High Avidity—*p*H				High Avidity Only			
					Pre	14	28	61	Pre	14	28	61
1	0·01 ml.	Bli.	28+?	6·2	<4	256	256		0	64	20	
L Sc, 2 ab	$4·2 \times 10^5$	Hou.	28	5·2	<4	256	4,096	1,024	0	0	320	200
	PFU	Mar.	21	5·7	<2	256	64	64	0	32	20	4
		Koc.	21	4·2	<2	1,024	512	256	0	320	320	320
		Gri.	21	3·7	<2	512	512	256	0	64	32	32
		Bur.	14	5·2	<2	2,048	1,024	512	0	320	320	320
		Dav.	14	4·2	<2	2,048	2,048	512	0	320	320	64
		Mil.	14	4·2	<2	2,048	2,048	2,048	0	2,000	320	320
		Lay.	14	3·7	<2	1,024	2,048	1,024	0	200	320	320
		Ell.	10	5·2	<2	1,024	512	256	0	64	200	200
		Kyz.	10	3·7	<2	512	512	256	0	64	32	32
		Oli.	10	4·2	<2	64	32	16	0	25	12	12
	0·001 ml.	Vas.	14	4·2	<4	64	16	<2	0	16	2	0
	$4·2 \times 10^4$	Sch.	10	4·2	<4	32	16	4	0	12	4	0
	PFU	Mor.	7	5·2	<2	16	<2	2	0	12	0	0
2	0·01 ml.	Est.	42	4·7	<2	256	256	128	0	32	32	20
		Pet.	21	4·7	<2	32	256	64	0	2	4	20
	$3·6 \times 10^5$	Fol.	14	4·7	<2	2,048	1,024	512	0	320	200	200
P 712, Ch, 2 ab	PFU	Sti.	10	4·2	<4	1,024	512	128	0	64	32	32
		Dan.	10	2·7	<2	32	16	8	0	16	4	2
3	0·01 ml.	Goo.	61+	5·7	<2	256	256	64	0	32	32	6
Leon 12 a_1b	$4·3 \times 10^8$	Tro.	61+	5·2	<2	32	32	16	0	0	0	2
	PFU	Put.	42	5·7	<2	32	128	64	0	0	3	4
		Cro.	42	5·2	<2	128	256	256	0	20	32	32
		Dor.	42	4·7	<2	32	32	64	0	0	0	3
		Nap.	28+	5·2	<2	2	1,024	64	0	0	32	6
		Eas.	28	5·2	<2	128	128	16	0	4	4	4
		Spo.	21	5·2	<2	<2	64	16	0	0	3	2
		Err.	21	4·2	<2	8	16	8	0	0	2	0
		Br.	14	4·7	<2	16	8		0	4	0	
		Har.	14	3·7	<2	64	64	64	0	4	32	6

It is now two years since the large lots of vaccine, currently used in progressively larger numbers, were first fed to human beings, and tests for persistence of antibody and resistance of the intestinal tract will shortly be carried out. Table IX shows the variation in antibody response of young adults and of antibody levels in individual persons during the first two months after ingestion of only one type of vaccine. The following points are especially worthy of note: (*a*) differences between low + high-avidity and high-avidity antibody titres at different times after infection; (*b*) the relatively low titres and occasionally absent high-avidity antibody following infection with the type 3 virus despite many weeks of extensive multiplication in the intestinal tract; (*c*) the transient antibody response in the three men who received the 10 times smaller dose of the type 1 vaccine, which was also associated with a much more limited extent of viral multiplication than is indicated by the peak titres of virus per gramme of stool that occurred for only a few days.

It is also important to note here that tests on five originally triple-negative children, who received 0.01-ml. doses of the same lots of vaccine seriatim at three-week intervals (1, 3, and 2), showed both more extensive and prolonged viral multiplication and higher titres of high-avidity antibody (Sabin, 1958). Thus, in the case of type 1 all were still excreting virus at 21 days, when further multiplication was cut off by the administration of the type 3 virus, and the high-avidity antibody titres 77 days after feeding were 3,200, 2,000, 2,000, 640, and 640. It is possible that these higher titres may in part at least be the result of the boosting effect of the subsequent infections with the types 3 and 2 viruses. While this may also be the explanation for the high-avidity antibody titres of 16, 16, 50, 64, and 200 against the type 3 virus, the same explanation cannot be invoked for the consistently higher titres of high-avidity antibody (200, 320, 320, 320, and 320) that were found in the five children against the type 2 virus, which was administered last. It is also noteworthy that both the duration of virus excretion and the amount of type 2 virus excreted per gramme of stool were greater in the children than in most of the adults (Sabin, 1958).

Effect of Multiple Doses of Salk Vaccine on Multiplication of Virus in Alimentary Tract and Immunogenic Effect of Orally Administered Attenuated Strains

The question has been raised whether "adequate" immunization with a *potent* formalinized vaccine of a high proportion of susceptibles in a country might not lead to the elimination of polioviruses from the community (Dick and Dane, 1958), and the relatively low incidence of poliomyelitis in the U.S.A. has been considered by some as reflecting the effect of the Salk vaccine not only on those who received it but also on the total dissemination of the polioviruses in the community. Studies on initially non-immune human beings who had been fed the three types of attenuated poliovirus after two doses of Salk vaccine (Sabin, 1956a, 1957a, 1958; Horstmann *et al.*, 1957a, 1957b) indicated no effect on the multiplication of the virus in the alimentary tract.

In the recent study of Clarke *et al.* (1958) in which type 3 attenuated virus was fed to 14 children who had previously had two doses of formalinized vaccine, 11 had naturally acquired type 3 antibody prior to the injections of the formalinized vaccine, and the other three had no high-avidity antibody; but natural infection with type 3 virus prior to the inoculation of formalinized vaccine cannot be excluded even in them, because no tests for low-avidity antibody were performed. Furthermore, these investigators fed a smaller dose of this virus in hard gelatin capsules, and since there were no controls for this dose and procedure in children without homotypic antibody, it is difficult to evaluate their results. It is noteworthy, however, that their records show that the virus multiplied for 31 days in two of the three children who had no naturally acquired high-avidity antibody and in only 3 of the 11 children with naturally acquired homotypic antibody for periods of 9, 14, and 14 days respectively. In my own tests with a somewhat larger dose of the type 3 virus given by mouth in syrup (instead of capsules), the incidence of infection in young adults with naturally acquired antibody was 50% (Sabin, 1957b).

A study on 25 children without naturally acquired type 1 or type 3 low- or high-avidity antibody (10 type 1 and 15 type 3) who were fed the corresponding attenuated strains after four doses of Salk vaccine was completed in my laboratory early in 1958 (in association with Drs. Krugman, Giles, Barnes, and Wang). The detailed results of this study (quoted in Sabin, 1958) have not yet been published, but have been made available to workers in this field. Four doses of Salk vaccine were used, because five months after the third dose (given about six months after the second) 4 of 9 (44%), originally without type 1 antibody, had no demonstrable type 1 antibody, and 10 of 19 (53%), originally without type 3, had no demonstrable type 3 antibody by the sensitive *p*H method.

The fourth dose consisted of an especially selected lot of high antigenic potency. Many of the children had titres of 128 and 256 three months after the fourth dose when they were fed 0.01 ml. of the same large lots of type 1 and type 3 attenuated vaccine, used in the studies on children without homotypic antibody. These higher antibody levels had no effect on either the amount or the duration of virus excretion in the stools. Variations in the expected patterns, suggesting interference with multiplication of the poliovirus in the intestinal tract of some of the children, were found to be associated with concurrent infections by various enteric viruses—for example, E.C.H.O. types 7 and 9, adenoviruses types 2 and 16, and two as yet unidentified viruses with properties distinct from the E.C.H.O., Coxsackie, and adenoviruses.

Pharyngeal Pollovirus

Nine of these children (four type 1 and five type 3) received a 10 times larger dose of virus, which on the basis of previous tests in young, non-immune adults was expected to result in virus multiplication in the throat of approximately 80%, and frequent tests for pharyngeal virus were carried out during a period of four weeks. Although all of these children excreted virus in the stools for periods of two weeks or longer, no virus was at any time found in the posterior pharyngeal wall. Since antibody may be expected to be present in the nasopharyngeal secretions of those with titres of about 25 or greater in the blood (Bell, 1948) one might have expected this interference with virus implantation in the throat of those possessing the higher levels of antibody.

However, two of this group of nine children, who had no demonstrable antibody, and one, who had only a titre of 4, at the time of virus feeding also exhibited no virus in the throat.

Despite this failure to correlate the results with the antibody status in the children, the uniformly negative findings in the tests for pharyngeal virus in this group strongly suggest that antibody produced by killed-virus vaccine can interfere with the localization and multiplication of polioviruses in the throat but not in the intestinal tract. It has also been pointed out elsewhere (Sabin, 1956b, 1958) that under natural conditions of infection with "viraemic" strains the high incidence of pharyngeal virus in patients with the clinical disease is more readily explained on the basis of secondary localization from the blood than on primary localization of ingested virus. On this basis one would expect that even minimal amounts of antibody in the blood engendered by killed-virus vaccine would be sufficient to block the secondary localization of "viraemic" polioviruses in the throat.

Those who assume that the throat is the major source of contagion with poliovirus among so-called "sanitary" populations (and the most casual observation indicates that small children of any socio-economic group are highly "unsanitary" human beings) would use such data to support the view that a killed-virus vaccine can influence the extent of poliovirus dissemination in a community. Actually, as has been pointed out elsewhere (Sabin, 1956b, 1958), the pharyngeal poliovirus is swept down into the stomach and is only rarely found in epidemiologically insignificant trace amounts in the mouth and saliva, and therefore cannot under ordinary circumstances be a significant source of contagion to others. Field studies during epidemic (Lipson *et al.*, 1956; Davis *et al.*, 1958) and non-epidemic periods (Fox *et al.*, 1958) have shown that the antibody produced by two or three doses of Salk vaccine does not interfere with the capacity of the individual to disseminate polioviruses.

Viral Multiplication in Intestinal Tract

It has been suggested (Salk, 1957) that an accelerated antibody response to natural infection in those previously immunized with formalinized vaccine may provide long-lasting immunity to paralysis even after demonstrable antibodies had disappeared from the circulation. Previous tests on adults (Sabin, 1957a, 1958) had revealed no evidence of either an accelerated or higher antibody response following infection with orally administered attenuated polioviruses in those who had been previously sensitized either by killed virus vaccine or by natural infection.

A further test of this question was carried out on 24 of the children in our recent study on the effect of four doses of Salk vaccine. Serum specimens were obtained five days after feeding of the attenuated polioviruses (because antibody is first detected in seven days in unsensitized persons), and in not a single instance was the titre of either high- or low-avidity antibody different from that in the serum taken immediately before feeding of the virus. In all instances multiplication of virus in the intestinal tract was later followed by a boost in antibody, but as regards the level of antibody ultimately achieved in these children as compared with those achieved in the initially triple-negative children who were fed the same doses of the same vaccines seriatim at three-week intervals without prior immunization by Salk vaccine (Sabin, 1958), the results were different for type 1 and type 3. In the type 1 group the very high titres of low-avidity antibody (512 to 4,096) were comparable to those obtained in the triple-negative children, but with few exceptions the titres of high avidity antibody were lower than in the triple-negative children. On the other hand, in the type 3 group the titres of both high-avidity (170–4,096) and low-avidity (256–4,096) antibody were strikingly higher than in the triple-negative children.

These studies clearly show that orally administered attenuated polioviruses are capable not only of greatly boosting the level of antibody but also of imparting the benefits of an intestinal infection in those who had already had four doses of commercially produced formalinized vaccine.

Field Trials Completed and in Progress with Aliquots of Large Lots of Types 1, 2, and 3 Attenuated Vaccines

The large lots of type 1 (L Sc, 2 ab), type 2 (P 712, Ch, 2 ab), and type 3 (Leon 12 a,b) attenuated poliovirus vaccine that are currently being used in field trials on increasingly larger numbers of children were prepared in December, 1956, and tested in small groups by different investigators in 1957 and 1958. The many preliminary tests on the triple-plaque-purified strains used for the preparation of these large lots were previously described (Sabin, 1957a, 1957b). Approximately 22 to 25 litres of each of the three types were prepared at the Merck Sharp and Dohme Research Laboratories in co-operation with Dr. Bettylee Hampil and her associates. Trypsinized rhesus kidney cells grown in 0.5% lactalbumin hydrolysate in Hanks's solution with 2% calf serum were used. After inoculation of the seed virus the maintenance medium consisted of 0.5% lactalbumin hydrolysate in Earle's solution gassed with CO_2 to a *p*H of about 7.5 without serum.

Ten per cent. of the bottles prepared from each lot of trypsinized monkey kidneys were left uninoculated and observed for the appearance of spontaneous simian viruses. No evidence of spontaneous virus activity was found in any of the original bottles, nor on passage of the harvested fluids to monkey kidney and human amnion cells. The passages in human amnion cells were carried out to check on the possible presence of measles virus. The harvested culture fluids were centrifuged and passed through K 6 and S 1 Seitz filter pads in series at room temperature. The Seitz-filtered fluids constitute the vaccine and have been stored at approximately $-20°$ C.

The tests prescribed by the American National Institutes of Health for aerobic and anaerobic bacteria, for tubercle bacilli in guinea-pigs, for lymphocytic choriomeningitis in mice, and for B virus in rabbits (10 ml. into each of six rabbits for each lot) were all carried out with negative results.

For the identification of the virus in each vaccine, as well as to check for the absence of non-poliomyelitic cytopathogenic viruses, specially potent poliovirus rabbit antisera were used. These rabbit antisera, in 0.1 ml. amounts, were capable of neutralizing approximately 10 million TCD_{50} of homotypic poliovirus, so that it was possible to test the undiluted vaccine

for the presence of other cytopathogenic viruses. No extraneous cytopathogenic virus was found by this method in any of the large lots of vaccine. The efficacy of this method was emphasized when similar tests on the large lot of Koprowski's type 1 "Chat" vaccine used in the Belgian Congo trials (Courtois *et al.*, 1958) revealed the presence of an unidentified, non-poliomyelitis cytopathogenic virus up to a 10^{-2} dilution of the culture fluid, but not in the higher dilutions.

The intracerebral and spinal tests for residual neurotropism in monkeys were reported previously (Sabin, 1957b; see also Table I). Additional intracerebral tests in 14 monkeys with the 10^{-1} and 10^{-2} dilutions of the type 1 vaccine, in search for evidence of a mixed population or of mutants originating in the monkeys, were also negative. Since these three strains are devoid of neurotropism for the mouse, the absence of this property was checked in each lot of vaccine by inoculating 20 adult mice with 0.02 ml. intraspinally. Although spinal inoculation of chimpanzees is not regarded as a necessary part of the testing of such a vaccine, each of the three lots was tested in three chimpanzees devoid of spontaneously acquired antibody for all three types of poliovirus. Chimpanzees with spontaneously acquired antibody for any of the three types of poliovirus might also have some lesions in the spinal cord, and therefore are not suitable for this type of test. Each chimpanzee was inoculated in the region of the lumbar enlargement (located by drawing a line across the lowest tips of the scapulae with the arms completely adducted) with 0.2 ml. of the undiluted culture fluid through an 18-gauge needle. Neither paralysis nor lesions in the spinal cord were found in any of the nine chimpanzees observed for a period of at least three weeks, and multiple sections through the lumbar cord indicated that the inoculum had been properly placed in the grey matter.

Potency of the Vaccines

The potency of each vaccine is determined by titration in cynomolgus monkey kidney tissue culture tubes, using 10 tubes for each tenfold dilution or five tubes for each threefold dilution. Comparative tests showed that rhesus cells yield lower titres (0.7 log for type 1, 0.3 log for type 2, and no significant difference for type 3), and that titres consistently higher by 0.3–0.5 log are obtained when the serum contained in the growth medium is leached out of the cells by leaving them in contact with serum-free medium for at least two hours. This is then replaced with fresh serum-free medium prior to the addition of the virus. The medium consists of 5% lactalbumin hydrolysate previously neutralized with NaOH to a *p*H of about 7.5 and diluted to 0.5% in Earle's solution (0.22% $NaHCO_3$), the final mixture being gassed with CO_2 to a *p*H of about 7.5. The virus-inoculated tubes are kept in a roller drum and the final readings are made eight days after inoculation. The Hsiung–Melnick technique in stoppered bottles was used for plaque counts, but the following modification in adsorption of the virus yielded two to three times higher counts with these particular attenuated strains: (*a*) the acid medium must be washed away by 5 ml. of alkaline medium, which is left on the cell sheet for about an hour and then removed prior to the addition of virus for adsorption; and (*b*) the virus must be diluted in maintenance medium containing 0.22% $NaHCO_3$ and at least 0.3 ml. added to each bottle in order to prevent the development of a highly acid fluid during the period of adsorption.

The type 1 vaccine has maintained its potency despite bottling at room temperature and storage at about −20° C. for two years—the most recent titres on various ampoules having yielded values of $10^{7.8}$ to $10^{8.1}$ TCD_{50} per ml. for the type 1 vaccine. The type 2 and type 3 vaccines have dropped somewhat in potency during this period from $10^{7.7}$ to $10^{7.3}$ TCD_{50} per ml. for type 2, and from $10^{7.9}$ to $10^{7.4}$ TCD_{50} per ml. for type 3. Tests carried out by Dr. P. A. D. Winter in my laboratory indicated that the 1:10 dilution of the vaccine used for feeding can be maintained in wet ice for at least a week without loss of titre.

The original tests that I carried out in 110 young adults and children were reported previously (Sabin, 1957b, 1958). Since that time I also fed these lots to 33 children and adults in various families, and to the 26 children in the study on the effect of multiple doses of Salk vaccine. The most detailed small-scale study on 178 children and adults in Leyden, Holland, was carried out in 1957 and 1958 by Professor J. D. Verlinde and his associates, who have recently published their results (Verlinde *et al.*, 1958).

Dr. M. Ramos-Alvarez and Professor Federico Gomez, of the Hospital Infantil in Mexico City, have carried out stepwise studies on progressively larger numbers of children, most of them under 5 years of age since May, 1957, and reported their results at the International Congress on Tropical Medicine at Lisbon, Portugal, in September, 1958. They began with 70 children, then increased the number to 200, and when no untoward reactions were observed in them or their contacts at home over a period of several months, they began early in 1958 a small-scale field trial on an additional 3,500 children who were given the three types of vaccine seriatim as described earlier. Although the number without homotypic antibodies for any one type varied with the age of the children, approximately 40 to 50% of the entire group were without homotypic antibodies prior to the ingestion of the vaccine. A most careful clinical surveillance failed to reveal any untoward reactions or illnesses attributable to the vaccines in these children or their contacts, and these investigators, in co-operation with the Ministry of Health in Mexico, have decided to start a much larger trial of aliquots of the same vaccines on approximately 500,000 children in three Mexican cities in February, 1959.

In June, 1958, Dr. Guillermo Contreras and Professor Arturo Scroggie, of Santiago, Chile, carried out a small-scale trial in 50 newborn children who received the three types of vaccine seriatim (1, 3, and 2 at four-week intervals). The results of antibody tests are not yet available, but they found no untoward effects in the children or their contacts (personal communication).

In October, 1958, Professor James H. Hale, of the University of Malaya, in Singapore, in co-operation with Dr. Doraisingham and others, of the Ministry of Health in Singapore, initiated a large-scale field trial in 200,000 children 3 months to 10 years of age. A serological survey previously carried out by Professor Hale indicated that the age at which 50% of the children had acquired antibodies for any one type was 7 to 10 years. The type 2 vaccine was administered first

because Singapore was at the time in the midst of a growing epidemic of exclusively type 1 paralytic poliomyelitis. The results soon to be reported by Professor Hale and his associates should be of special interest because of the light they may throw on the extent of interference and protection that an infection with type 2 virus may exert against the paralytic effects of an epidemic strain of type 1 poliovirus, not only in the vaccinated children but also in the remainder of the population. Both Professor Hale and I were against using the type 1 attenuated poliovirus in the midst of a type 1 epidemic, before the safety of the vaccine had been established on a sufficiently large scale under non-epidemic field conditions.

Another large-scale field trial with aliquots of these large lots of vaccine designed to test the effectiveness of combined killed-virus and live-virus vaccine immunization was begun by the Ministry of Health in Czechoslovakia in December, 1958, under the direction of Drs. Skovranek, Raska, Prochazka, Zacek, and Slonim. Almost all children under 12 years of age in Czechoslovakia had received Salk vaccine (predominantly of Canadian manufacture) in 1957 and 1958. The approximately 143,000 children 2 to 7 years of age in four different regions of the country involved in this trial had previously received three 0.2-ml. intracutaneous doses of formalinized vaccine at the proper intervals in 1957 and 1958. The type 1 oral attenuated vaccine was administered during the course of a few days beginning December 15, 1958, and the type 3 vaccine beginning January 12, 1959; the type 2 vaccine is scheduled for four weeks after the type 3. Serological surveys prior to and after the administration of these vaccines, as well as the careful long-range clinical and virological surveillance of the vaccinees and their contacts, that have been organized by the Czechoslovak investigators should provide us with important information of the greatest significance for the ultimate control of poliomyelitis.

Approximately 225,000 doses of aliquots of each of the three lots of vaccine have been supplied to Professors Chumakov and Smorodintsev in the U.S.S.R. for large-scale trials that began late in 1958. Small-scale studies by Professor J. Fox and his associates, of Tulane University, and by Professor J. R. Paul and his associates, of Yale University, in the U.S.A., and by Professor M. Kitaoka, of the National Institute of Health in Japan, with aliquots of the same lots of vaccine are also expected to contribute valuable information for the ultimate evaluation of the behaviour of these particular strains in human beings.

The expert committee on poliomyelitis of the World Health Organization (1958), in the portion of its July, 1957, report dealing with live virus vaccine, stated: "It is the carefully considered opinion of the committee, therefore, that the information which is now badly needed can only be obtained from field trials carried out on a larger scale than has been possible in the past," and laid down specifications for the strains of virus and the lots of vaccine to be used in such trials as well as the manner in which they should be performed. The large lots of vaccine here described fulfil these specifications, and it is hoped that the large-scale field trials now in progress, and still others yet to come, may provide the answer regarding the ultimate safety and usefulness of live virus vaccine in the prevention and eradication of poliomyelitis.

C

Summary

The reasons why one cannot speak of a return to virulence in polioviruses, based merely on the finding that large doses of poliovirus produce paralysis in a varying proportion in intracerebrally inoculated monkeys, are analysed and discussed. The proper measurement of different grades of neurotropism in monkeys, only one of the factors determining the virulence of ingested polioviruses in higher primates, is dependent on the employment of certain specified techniques which are suitable for measuring the varying capacity of polioviruses for spreading from one group of initially exposed susceptible cerebral or spinal neurones to another. Although the best attenuated strains, developed thus far, still have a limited residual neurotropism for the spinal motor neurones of the monkey, they produce neither paralysis nor lesions in chimpanzees properly inoculated in the spinal cord. Furthermore, viruses that are distinctly paralytogenic after intracerebral inoculation of moderate doses in monkeys are not paralytogenic on proper spinal inoculation of large doses in chimpanzees.

Additional data on the neurotropism of the polioviruses excreted in the stools following ingestion of the most highly attenuated currently available strains indicate: (*a*) that a certain proportion of the viral population (more so with type 3 than types 1 and 2) is less attenuated than that which was ingested, that portion being selectively detected by inoculation in the nervous system of monkeys; (*b*) that the less attenuated virus is not selectively propagated in the human alimentary tract, as is evident from the disappearance of such virus after prolonged multiplication in the intestinal tract of the original vaccinees, and the failure to find progressive increase in neurotropism after further multiplication in the intestinal tract of naturally exposed contacts, or after repeated experimental passages in human beings. These findings are the main reason for utilizing the most highly attenuated strains, possessing an adequate capacity for multiplication in the human intestinal tract, for vaccines to be used in large-scale trials in human beings.

The antibody response to the feeding of live attenuated polioviruses has been shown to depend on the dose, strain, and extent of multiplication in the intestinal tract. Persistence of detectable antibody is not dependent on the titre achieved, and resistance of the alimentary tract has been shown to be present even in the absence of readily demonstrable antibody.

Multiple doses of Salk vaccine, currently produced commercially in the U.S.A., often fail to produce an adequate antibody response and the persistence of the antibody is dependent on the level originally produced. However, even high levels of antibody produced in some children by four doses of Salk vaccine failed to influence in any way the extent of viral multiplication in the intestinal tract, although localization and multiplication in the throat was apparently prevented. The available evidence, however, indicates that virus in the throat is of little or no importance in the transmission of infection to others. No evidence was found that previous immunization with Salk vaccine results in an accelerated antibody response to multiplication of orally administered polioviruses, and there is therefore no theoretical basis for expecting long-lasting immunity from a formalinized vaccine after the initially produced antibody has disappeared.

Studies on progressively increasing numbers of children, with aliquots of large lots of vaccine prepared

in December, 1956, with the most highly attenuated currently available strains of each of the three types, have thus far produced no untoward reactions in vaccinees or their contacts. Spread of the vaccine viruses to others is an accepted fact in the immunization with live poliovirus vaccines, and this problem is not being "side-stepped" but is rather being carefully studied in various trials. The trials on some hundreds of thousands of children—some already completed, others now in progress, and still others to be initiated in 1959—carried out in accord with the stipulations of the Expert Committee on Poliomyelitis of the World Health Organization should provide us in the near future with the information necessary for a decision regarding the place of orally administered live poliovirus vaccines in the prevention and eradication of poliomyelitis.

REFERENCES

Bell, E. J. (1948). *Amer. J. Hyg.*, **47**, 351.
Bodian, D., Morgan, I. M., and Schwerdt, C. E. (1950). Ibid., **51**, 126.
Clarke, S. K. R., Goffe, A. P., Stuart-Harris, C. H., and Herzog, E. G. (1958). *Brit. med. J.*, **2**, 1188.
Courtois, G., Flack, A., Jervis, G. A., Koprowski, H., and Ninane, G. (1958). Ibid., **2**, 187.
Dane, D. S., Dick, G. W. A., Briggs, M., and Nelson, R. (1958). Ibid., **2**, 1187.
Davis, D. C., Lipson, M. J., Carver, D. H., Melnick, J. L., and Robbins, F. C. (1958). *Pediatrics*, **22**, 33.
Dick, G. W. A., and Dane, D. S. (1957). *Brit. med. J.*, **1**, 70.
—— —— (1958). Ibid., **2**, 1184.
Fox, J. P., Gelfand, H. M., LeBranc, D. R., and Conwell, D. P. (1957). *Amer. J. Hyg.*, **65**, 344, 367.
—— —— —— and Rowan, D. F. (1958). *Amer. J. publ. Hlth*, **48**, 1181.
Horstmann, D. M., Niederman, J. C., Melnick, J. L., and Paul, J. R. (1957a). *Trans. Ass. Amer. Phys.*, **70**, 91.
—— Paul, J. R., Melnick, J. L., and Deutsch, J. V. (1957b). *J. exp. Med.*, **106**, 1959.
Hsiung, G. D., and Melnick, J. L. (1958). *J. Immunol.*, **80**, 282.
Kanda, Y., and Melnick, J. L. (1958). *J. exp. Med.*, **109**, 9.
Leading article (1958). *Brit. med. J.*, **2**, 1210.
Le Bouvier, G. L. (1957). *Amer. J. Hyg.*, **66**, 342.
Lennette, E. H., and Schmidt, N. J. (1957). Ibid., **65**, 210.
Li, C. P., and Jahnes, W. G. (1958). *Fed. Proc.*, **17**, 522 (abstract).
Lipson, M. J., Robbins, F. C., and Woods, W. A. (1956). *J. clin. Invest.*, **35**, 722.
Sabin, A. B. (1955a). *Ann. N.Y. Acad. Sci.*, **61**, 924.
—— (1955b). *Amer. J. med. Sci.*, **230**, 1.
—— (1956a). *J. Amer. med. Ass.*, **162**, 1589.
—— (1956b). *Science*, **123**, 1151.
—— (1957a). *Special Publications of the New York Academy of Sciences*, **5**, 113.
—— (1957b). *J. Amer. med. Ass.*, **164**, 1216.
—— (1958). *Advanc. Pediat.*, **10**, 197.
—— Hennessen, W. A., and Winsser, J. (1954). *J. exp. Med.*, **99**, 551.
Salk, J. E. (1957). *Amer. J. publ. Hlth*, **47**, 1.
da Silva, M. M., McKelvey, J. L., Bauer, H., Prem, K. A., Cooney, M. K., and Johnson, E. A. (1957). *Univ. Minn. med. Bull.*, **29**, 133.
Smorodintsev, A. A., Davidenkova, E. F., Drobishevskaya, A. I., Ilienko, V. I., Gorev, N. E., Kuriosova, L. M., Kluchareva, T. E., and Alekseyev, B. P. (1958). In Problems of Poliomyelitis, Abstracts of Scientific Sessions at Institute of Infectious Diseases in Kiev, March 26-29, 1958; also presented in discussion at International Congress on Tropical Medicine, Lisbon, Sept. 1958.
Verlinde, J. D., Wilterdink, J. B., Hofman, B., and Kret, A. (1958). *Ned. T. Geneesk.*, **102**, 1144. Also *Arch ges. Virusforsch.*, in press.
Vogt, M., Dulbecco, R., and Wenner, H. A. (1957). *Virology*, **4**, 141.
World Health Organization (1958) *Wld Hlth Org. techn. Rep. Ser.*, No. 145

RESPONSE OF INFANTS TO A THIRD DOSE OF POLIOMYELITIS VACCINE GIVEN 10 TO 12 MONTHS AFTER PRIMARY IMMUNIZATION

BY

F. T. PERKINS, M.Sc., Ph.D.

RISHA YETTS, B.Sc.

From the Biological Standards Control Laboratory, Medical Research Council Laboratories, London, N.W.3

AND

WILFRID GAISFORD, M.D., M.Sc., F.R.C.P.

Director of the Department of Child Health, University of Manchester

In our first study (Perkins, Yetts, and Gaisford, 1958) we reported that when infants aged 10 weeks or less were given a primary course of two doses of poliomyelitis vaccine the antibody response was in most cases unsatisfactory. This was due principally to the inhibiting effect of maternally transmitted antibodies, but also to the fact that a stronger antigenic stimulus is necessary in the newborn period to produce results comparable with those obtained in later infancy.

Despite the unsatisfactory results it was thought possible that, in at least some of the infants, primary immunization might have occurred but that we had been unable to demonstrate this because the increase in antibody level had been masked by the maternally transmitted antibodies. It was therefore decided to recall the infants approximately a year later and, from a study of the response to a reinforcing dose, obtain further information on the extent of any basal immunity which had been induced.

Procedures

Immunization.—Of the 88 infants previously studied, 80 were available. They were given 1 ml. of vaccine intramuscularly 10 to 12 months after their second dose. The vaccine used was Glaxo batch 13, which had been shown to have satisfactory antigenic activity by the routine test in monkeys (Biological Standards Control Laboratory, 1957). The infants, who were 1, 6, and 10 weeks old respectively at the time of injection of the first dose of vaccine, were designated as groups A, B, and C. In the present investigation there were 29 in group A, 28 in group B, and 23 in group C.

Titration of Sera.—The sera were titrated for poliomyelitis-neutralizing antibodies to each of the three virus types by the method previously described (Biological Standards Control Laboratory, 1957), which has been shown to give reproducible results (Perkins, Sousa, and Tobin, 1958). Fourfold serial dilutions of sera were used, the test dose of virus was approximately 100 $TCID_{50}$, and each serum-dilution/virus mixture was inoculated into two monkey-kidney-cell culture tubes. The two samples of serum from each infant were titrated in parallel in the same test, together with a repeat titration of the serum sample taken 14 to 21 days after the second dose. In the case of one infant in group B it was not possible to determine antibody levels to types 2 and 3 virus. All titres are given as the dilution of serum in the serum–virus mixtures before addition to cell cultures

Level of Antibody 10 to 12 Months After Two Doses of Vaccine

Almost all the infants who had not given a serological response to two doses of vaccine had either undetectable or very low antibody levels 10 to 12 months later. This was the case for all three virus types and for each age group. However, in most of those infants who had responded to primary immunization the titres had not fallen comparably, the antibody produced in response to active immunization having clearly been lost at a slower rate than the maternally transmitted antibody.

In 17 of the infants the antibody levels at the time of giving the booster dose were higher than those present immediately after the second dose—seven were in group A, five in group B, and five in group C. Of these 17 infants, eight had increased antibody levels to two types of virus and nine to one type. In all, there were eight with increased levels to type 1, nine to type 2, and eight to type 3. The increases were evenly distributed between infants who had responded to primary immunization and those who had not. In all cases the response to the booster dose was very high to the type in which the increase had occurred and much higher than the response of the remainder of the infants. These findings made it likely that intercurrent non-paralytic infection had occurred in these 17 infants, and they were therefore excluded from the analysis of the results. The infants remaining in the final analysis were 22 in group A, 23 in group B, and 18 in group C.

Response to a Booster Dose of Vaccine

The responses to the three virus types after receiving the booster dose are shown in Figs. 1, 2, and 3. The antibody titres of those infants who had responded to primary immunization—"primary responders"—are shown as open circles, and the titres of those who had not are indicated by black circles. The response to type 1 (Fig. 1) by the 22 infants in group A was very poor. None of these infants were primary responders and only five gave a small increase in antibody titre after the booster dose, the highest being 32. The results in groups B and C were better, 17 responding in group B and 16 in group C. The level in many, however, was not as high as would be expected if the infants had been sensitized by primary immunization.

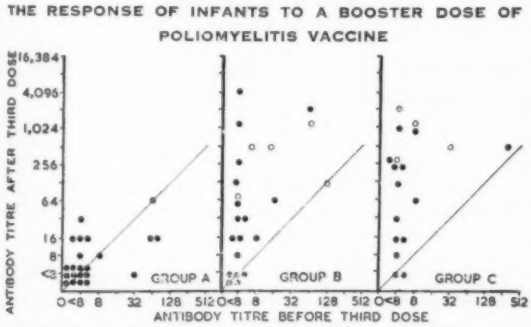


FIG. 1.—Serological response of 1-, 6,- and 10-weeks-old infants to type 1 virus. O=Infants previously responding to primary immunization. ●=Infants previously *not* responding to primary immunization.

Of the 32 infants in these two groups who were not primary responders, 20 had antibody levels of 64 or less, which were poor in comparison with the primary responders, all of whom had titres of 64 or more after the booster dose. Of the nine primary responders, eight showed increases in titre after the booster dose, the smallest increase being from <8 to 64 and the highest from <8 to 2,048. The remaining primary responder, who showed no increase, had a titre of 128 both before and after the booster dose. It is thus evident that the primary responders produced better levels after the booster dose than the majority of those who had not responded to primary immunization. Nevertheless, in groups B and C there were infants who had shown no apparent primary response but whose titres after the booster dose were as high as some of the primary responders. In all these subjects, however, the maternal antibody levels at the time of primary immunization were 256 or less.

The responses to type 2 (Fig. 2) show also that the older infants reacted better than the younger ones. Of the 62 infants in all, only seven failed to respond, five of whom were in group A and two in group B. In group A, all six primary responders gave higher antibody levels than all but 2 of the remaining 16 in the group, 5 of whom gave antibody levels of less than 64. In group B, 7 of the 10 primary responders gave antibody levels higher than all but 3 of the remaining 12 in the group. In group C, however, the seven infants who gave no apparent primary response gave as high antibody levels to the booster dose as the 11 primary responders.

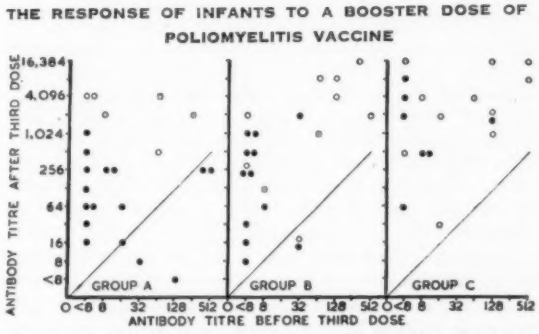


FIG. 2.—Serological response of 1-, 6-, and 10-weeks-old infants to type 2 virus.

The responses to type 3 (Fig. 3) were similar to those obtained to type 2. The three primary responders in

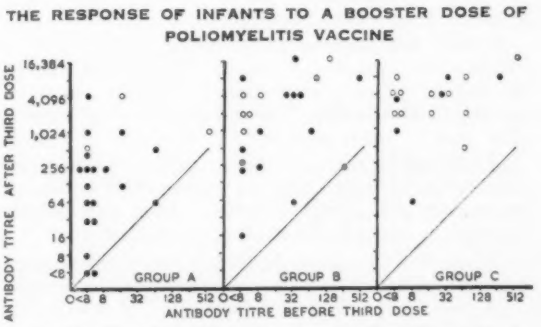


FIG. 3.—Serological response of 1-, 6-, and 10-weeks-old infants to type 3 virus.

group A gave higher antibody levels than 14 of the remaining 19 in the group, 3 of whom gave no response. In group B the primary responders gave antibody levels higher than some of the non-responders, whereas in group C this was not the case because the response to the booster dose was similar in both the primary responders and non-responders.

Discussion

These results of the responses of infants to a booster dose of vaccine give a clearer picture of the influence of maternally transmitted antibodies on primary immunization. High levels of such antibody completely inhibit active immunization against the homologous type. No infant with an antibody level of 1,024 or more before primary immunization gave a secondary response to the booster dose, indicating that primary immunization had been ineffective. This was true for all three virus types, although a high level of maternal antibody to one type had no inhibiting effect on the response to either of the heterologous types. Infants who had apparently not given a primary response, but whose secondary response was as good as that of the primary responders, had maternally transmitted antibody levels between 32 and 1,024; clearly these levels had not completely inhibited, but had merely masked, the primary response. Infants with low maternal antibody levels who had responded to primary immunization showed a good response to the booster dose. There were, however, a number who, in spite of the fact that they had low levels of transmitted antibody, did not respond initially — the "poor responders"—and these gave a similarly poor response to the booster dose.

It is also evident from the results that the best response is given by the 10-weeks-old infants, but these can by no means be regarded as satisfactory, and compare unfavourably, especially for type 1, with those obtained in 1- to 9-year-old children (Medical Research Council, 1957a, 1957b).

These results substantiate our initial conclusions that immunization in the first few weeks of life is unsatisfactory, especially to the type 1 virus. In order to be effective, primary immunization should produce substantial antibody responses to all three types in order to ensure an adequate secondary response to the booster dose. This is not likely to be achieved with existing vaccines unless immunization is delayed until the maternal antibody has fallen to a low non-inhibitory level, which may not be until the infants are 6 to 9 months old. These age groups are at present being studied.

Summary

A study was made of the effect of a third dose of poliomyelitis vaccine in a group of 80 infants who at the time of primary immunization were 10 weeks of age or less. The booster dose was given 10 to 12 months after primary immunization.

In 17 infants a rise in antibody titre occurred between primary immunization and the booster dose, indicating intercurrent poliomyelitis infection. These infants were excluded in assessing the effect of the booster dose.

Infants who showed an increase in antibody level after primary immunization also responded to the booster dose, but they all had low levels of maternally transmitted antibody. Those with high antibody levels at birth who gave no primary response did not react to the booster dose. A number with intermediate levels of maternal antibody who showed no apparent primary response reacted to the booster dose; in these, primary immunization had evidently occurred, but the rise in titre was masked by the maternal antibody.

In general, the infants who had started their primary immunization at 10 weeks of age responded better to the booster dose than those starting at 1 and 6 weeks old.

This study confirms our original conclusion that immunization of infants against poliomyelitis in the first few weeks of life cannot be regarded as satisfactory, especially with regard to the response to type 1 virus. It is possible that the earliest age when satisfactory mass immunization may be achieved is when the infant is 6 to 9 months old. This age group is at present being studied.

Our thanks are due to Dr. G. V. Feldman, Dr. R. F. Jennison, and the nursing and laboratory staff at St. Mary's Maternity Hospital, Manchester, for their assistance, and to Miss K. South and Miss P. Tumber, of the Biological Standard Control Laboratory, London, for their help in titrating the sera. We also thank the Ministry of Health for the supply of poliomyelitis vaccine. This work was supported in part by a grant from the National Fund for Poliomyelitis Research to the Department of Child Health, Manchester University, for which we are most grateful.

REFERENCES

Biological Standards Control Laboratory (1957). *Brit. med. J.*, **2**, 124.
Medical Research Council (1957a). Ibid., **1**, 366.
—— (1957b). Ibid., **2**, 1207.
Perkins, F. T., Sousa, C. A. P., and Tobin, J. O'H. (1958). *Brit. J. exp. Path.*, **39**, 171.
—— Yetts, R., and Gaisford, W. (1958). *Brit. med. J.*, **2**, 68.

SIDE-EFFECTS FOLLOWING TRIAMCINOLONE

BY

P. HUME KENDALL, M.R.C.P., D.Phys.Med.

Senior Registrar, Guy's Hospital, and Orpington Hospital, Kent

AND

MAURICE F. HART, M.D., M.R.C.P.

Consultant in Physical Medicine, Farnborough Hospital, Kent

The initial reports on the use of triamcinolone (16α-hydroxy, 9α-fluorohydrocortisone) as a suppressive agent in rheumatoid arthritis were extremely encouraging. Originally announced by Hellman *et al.* (1957) at the American Rheumatism Association meeting at Bethesda in 1956, it was stated to possess powerful antirheumatic properties. They claimed that an average dose of 13.5 mg. daily resulted in a response superior to that observed with other steroids; metabolic balance studies suggested that little or no sodium retention or potassium or nitrogen loss occurred, and at that time no undesirable side-effects had been noted. Bunim (1957) agreed with these findings, but warned that it was much too early to draw any conclusions, as at that time only a few patients had been treated for short periods.

Later reports suggest that the side-effects normally associated with steroid therapy do in fact follow the prolonged administration of triamcinolone. Hollander

(1957), as well as being unable to confirm that the clinical potency of the drug was any greater, dose for dose, than prednisone or prednisolone, noted that, out of six patients observed, two experienced dyspepsia, three anorexia, and all lost weight. Three of his patients reverted to their original steroid because of increasing symptoms and signs of arthritis despite increased dosage. Dudley Hart *et al.* (1958) found that 2 out of 27 patients developed Cushingoid facies and striae, one suffered crush fractures of the ribs and lumbar vertebrae, three suffered from dyspepsia, and one had a perforated gastric ulcer. Three patients in his series suffered from "postprandial flushings" and one developed hypertension. They concluded that, although triamcinolone is a useful steroid, it does not differ greatly from prednisolone in its therapeutic action or in its undesirable side-effects.

Thus it appears that there still exists controversy over the relative potency of triamcinolone as well as over the incidence of side-effects in patients on long-term therapy. It was thought worth while, therefore, to report the clinical progress and side-effects observed in a series of 47 patients suffering from rheumatoid arthritis who have been treated continuously with the drug for periods varying from 5 to 11 months.

Selection of Patients

The two hospitals at which the present series of patients were treated lie in the centre of a densely populated residential area, approximately 15 miles (24 km.) from the centre of London. As a result, many of the patients suffering from rheumatoid arthritis are living at home, having retired or been forced by the ravages of their disease to give up work. Furthermore, many of them have visited other specialist centres in the past, and undergone numerous forms of treatment. We are therefore only too frequently faced with the severely disabled and dispirited patient with overwhelming rheumatoid disease, often further complicated by visceral manifestations, who sits at home and loses all interest in life. We feel that the administration of steroids as a part of the medical treatment of selected patients in this group is essential if they are to be satisfactorily rehabilitated.

The majority put on to triamcinolone were already undergoing treatment with prednisone or cortisone, and were changed to the new drug either as a result of diminishing clinical response to increasing dosage or on the appearance of side-effects.

No special precautions were taken to prevent the patients knowing that they were on a new drug, the main object throughout being to obtain the maximum therapeutic benefit for each individual. Thus the observations made cannot in any way be said to result from a specifically controlled trial; they are nevertheless of value inasmuch as they relate to a special group of patients who have been treated for a longer period with the new steroid than any others so far reported.

Details of Patients in the Order in which they were put on to Triamcinolone

Case No.	Age	Sex	Duration of Disease	Mean Dose	Initial	Subsequent	Present Status	Total Period of Observation	Side-effects
1	63	M	4 years	16 mg.	Good	Well maintained	Continuing	11 months	Mooning, flushing
2	36	M	10 ,,	12 ,,	,,	Deteriorated	On prednisone	10 ,,	Mooning, fractured ribs, flushing
3	58	M	16 ,,	12 ,,	Poor	Poorly maintained	Continuing	10 ,,	Mooning, dyspepsia, flushing
4	56	F	4 ,,	16 ,,	Good	Well maintained	,,	10 ,,	Calf-wasting, flushing, mooning, loss of weight
5	39	F	5 ,,	4 ,,	,,	,, ,,	,,	10 ,,	Nil
6	72	M	10 ,,	4 ,,	,,	,, ,,	,,	10 ,,	,,
7	59	F	1 year	4 ,,	,,	,, ,,	,,	10 ,,	Depression
8	49	M	4 years	8 ,,	,,	Deteriorated	On prednisone	7 ,,	Severe dyspepsia
9	31	F	11 months	8 ,,	,,	Well maintained	Continuing	8 ,,	Flushing
10	83	F	14 years	4 ,,	,,	,, ,,	,,	8 ,,	Nil
11	74	F	11 ,,	12 ,,	Poor	Improved	,,	7 ,,	Loss of weight, dyspepsia
12	48	F	5 ,,	6 ,,	Good	Well maintained	,,	7 ,,	Nil
13	63	F	13 ,,	8 ,,	,,	,, ,,	,,	7 ,,	Flushing, mooning
14	75	M	2 ,,	4 ,,	,,	,, ,,	,,	7 ,,	Nil
15	67	F	6 ,,	8 ,,	Poor	Improved	,,	6 ,,	,,
16	71	F	7 ,,	4 ,,	Good	Well maintained	,,	6 ,,	,,
17	30	F	4 ,,	4 ,,	,,	,, ,,	,,	6 ,,	,,
18	60	F	20 ,,	6 ,,	,,	,, ,,	,,	6 ,,	Mooning flushing, oedema
19	50	F	1 year	8 ,,	Poor	Failed to respond	On prednisone	5 ,,	Flushing, fractured metatarsal
20	55	F	5 years	4 ,,	Good	,, ,, ,,	,, ,,	6 ,,	Nil
21	43	F	5 ,,	4 ,,	,,	Well maintained	,, ,,	5 ,,	Dyspepsia, loss of weight
22	58	F	10 ,,	8 ,,	,,	Deteriorated	On medrol	5 ,,	Muscle-wasting, mooning, flushing
23	48	F	6 months	12 ,,	,,	Well maintained	Continuing	6 ,,	Cushingoid, muscle-wasting, depression
24	54	M	2 years	6 ,,	,,	,, ,,	,,	6 ,,	Nil
25	46	F	8 ,,	6 ,,	,,	,, ,,	,,	6 ,,	,,
26	40	M	6 ,,	4 ,,	,,	,, ,,	,,	6 ,,	,,
27	68	F	13 ,,	4 ,,	,,	,, ,,	,,	6 ,,	,,
28	51	F	3 ,,	6 ,,	,,	,, ,,	,,	6 ,,	,,
29	53	F	5 ,,	6 ,,	,,	,, ,,	,,	6 ,,	Flushing
30	47	M	20 ,,	4 ,,	,,	,, ,,	,,	6 ,,	,,
31	47	F	1 year	4 ,,	,,	,, ,,	,,	5 ,,	,,
32	64	F	20 years	4 ,,	,,	,, ,,	,,	5 ,,	Flushing, loss of weight
33	42	M	6 months	4 ,,	,,	,, ,,	,,	5 ,,	Nil
34	30	F	1 year	8 ,,	Poor	Poor response	Off steroids	5 ,,	,,
35	62	F	3 years	8 ,,	Good	Well maintained	Continuing	5 ,,	Loss of weight, depression
36	72	F	24 ,,	12 ,,	Poor	Poor response	On prednisone	4 ,,	Mooning, dyspepsia, flushing
37	64	F	8 ,,	12 ,,	,,	,, ,,	On medrol	3 ,,	Cushingoid, calf-wasting, flushing
38	54	F	1 year	8 ,,	Good	Well maintained	Continuing	8 ,,	Flushing, depression
39	61	F	5 years	4 ,,	,,	,, ,,	,,	5 ,,	Nil
40	27	M	7 ,,	8 ,,	,,	,, ,,	,,	5 ,,	,,
41	53	M	1 year	12 ,,	Poor	Improved	,,	5 ,,	,,
42	51	M	5 years	10 ,,	Good	Well maintained	,,	5 ,,	Flushing
43	40	F	1 year	4 ,, b.d.	Poor	Deteriorated	Off steroids	3 ,,	Nil
44	47	M	2 years	4 mg.	Good	Well maintained	Continuing	5 ,,	,,
45	61	M	20 ,,	4 ,,	,,	,, ,,	,,	5 ,,	Flushing, dyspepsia
46	31	M	8 ,,	12 ,,	,,	,, ,,	,,	5 ,,	Flushing, mooning
47	54	F	12 ,,	8 ,,	,,	,, ,,	Off steroids	5 ,,	Haematemesis

As a rule each patient has been seen at fortnightly intervals, although in some cases the intervening periods have been longer, where patients lived some distance from the hospitals and their general practitioner was prepared to take over maintenance.

At each attendance a full subjective and objective assessment was made, being based on joint tenderness, joint range, and walking-time for a given distance. A detailed search for side-effects was carried out, and repeated examinations of the erythrocytic sedimentation rate and electrolytes were undertaken. Details of the 47 patients are given in the Table.

Results

Of the 47 patients who began treatment with triamcinolone, 36 are still maintained on the drug. Of the 11 who were taken off, seven had deteriorated rapidly, and four suffered from side-effects severe enough to merit cessation of the drug. Of those that deteriorated, six are now well maintained on prednisolone, two on 6-methyl prednisolone, and three have ceased steroid therapy altogether.

Altogether 24 patients have experienced side-effects: of these, the commonest is facial and body flushing, which occurred in 17 patients. The facial appearance is quite typical, and is distinct from that usually associated with high dosage of the other steroids. The skin of the whole face from the hair-line down to the neck appears to be involved, and becomes a uniform bright pink colour, the whole picture being so characteristic that it has merited the term "triamcinolone face" amongst the nursing and physiotherapy staff.

"Mooning" of the face was observed in nine patients; two of these exhibited marked hirsuties within six to eight weeks of starting treatment. Eight suffered from dyspepsia, and one of the latter developed haematemesis and melaena within 24 hours of the first symptoms of dyspepsia. Mental depression occurred in four patients, but in none was its character severe enough to merit stopping the drug. In two patients spontaneous fractures occurred. These were of the ribs and a metatarsal bone respectively; both had been on prednisone for a considerable period prior to the triamcinolone. Severe weight loss—more than 14 lb. (6.4 kg.)—occurred in five of the patients, and in four the phenomenon of rapid symmetrical muscle-wasting was observed. In three this involved predominantly the leg muscles, and in two the arms and shoulders. In all, these symptoms appeared within three months of commencing the triamcinolone, and in two the condition has deteriorated slightly on continued therapy; in the other two, muscle bulk and power have returned on reverting to alternative steroids.

With respect to the clinical suppression of the symptoms of the rheumatoid arthritis, 36 patients continue to be well maintained and are continuing with treatment despite the presence of minor side-effects in a small number.

Discussion

As with other observers, we agree that there appears to be little to choose between triamcinolone and other available steroids in relation to its potency in arthritis, particularly where high dosages are concerned. The incidence of side-effects following long-term therapy, however, seems to be as high as if not higher than that normally expected from prednisone. Only one patient out of 11 on a dosage of 12 mg. daily or higher was free of side-effects after a period of five months or longer. The dangers of gastro-intestinal haemorrhage, and the chances of developing a Cushingoid syndrome or hirsuties, moonface, and facial flushing (see illustration) still appears to be as great as they are with prednisone or prednisolone.

Local muscle-wasting, the cause of which is rather puzzling, is a new complication to follow steroid therapy. K. S. MacLean (1958, personal communication) has reported a similar case following prolonged treatment with large doses of 9α-fluorohydrocortisone, and suggests that the fluorine atom present in the 9α-position in both drugs may be responsible for this property. The disability that results from this complication can be severe, and the problem obviously requires further elucidation. In our view the weight loss that sometimes occurs is not necessarily a handicap, for many of the patients we see are considerably overweight. It may well be that there is a place for alternating, say, prednisone and triamcinolone over periods of one or two months to counterbalance the opposing tendencies of each drug.

Case 23. Cushingoid facies six weeks after starting on triamcinolone. Hirsuties also present.

Perhaps the most significant feature of the results obtained from the series so far is the relative lack of complications following the administration of 6 mg. or less of triamcinolone daily. Only three patients out of 23 on this dosage suffered any discomfort, and all continue to be well maintained on the drug. This dose has given a good clinical result in a considerable number of patients, and it is our impression that the response is much greater than that following the equivalent dosage of prednisone and prednisolone (5–7.5 mg.). It is our rule now to begin therapy on a dosage of 4 mg. daily, increasing it to 6 mg. if necessary, but avoiding greater dosages if possible. At present we feel that this is the highest level at which therapy can be safely prolonged. Only increasing experience will show whether serious side-effects will eventually follow this small dose. If they do not the fact that such a good clinical response can be obtained in this way will certainly make triamcinolone an extremely valuable drug in the treatment of rheumatoid arthritis.

Summary

The clinical progress of 47 patients treated with triamcinolone in doses of up to 16 mg. daily, for periods of up to 11 months, is reviewed.

Altogether, 24 patients had experienced serious side-effects, the majority of which resemble those seen following other steroids. Four patients suffered muscle-wasting, the causation of which is not obvious.

Of the patients receiving less than 6 mg. a day, only three suffered any discomfort, and it is suggested that this is the highest maintenance dose which can be prolonged.

We thank Dr. M. E. Fearnley, Consultant to the Physical Medicine Department, Orpington Hospital, Kent, for being allowed to report on his patients, and the pharmacists at both hospitals for obtaining supplies in the early stages. We are also indebted to the many local practitioners who have co-operated so willingly with us.

REFERENCES

Bunim, J. J. (1957). *Ann. rheum. Dis.*, **16**, 142.
Hart, F. D., Golding, J. R., and Burley, D. (1958). *Lancet*, **2**, 495.
Hellman, L., Zumoff, B., Schwartz, M. K., Gallagher, T. F., Berntsen, C. A., and Freyberg, R. H. (1957). *Ann. rheum. Dis.*, **16**, 141.
Hollander, J. L. (1957). Ibid., **16**, 142.

CIRCULATORY EFFECTS OF TRUMPET PLAYING

BY

M. FAULKNER, Ph.D.
Associate Professor of Music, University of California, Santa Barbara

AND

E. P. SHARPEY-SCHAFER, F.R.C.P.
Professor of Medicine, St. Thomas's Hospital, London

It is well known among professional trumpeters that playing high loud notes for more than a few seconds may cause dizziness or occasionally "black-out." Indeed, many leading orchestras carry an assistant or "mate" to take over from the first trumpet in prolonged difficult passages. All are agreed that Wagner is the composer with least consideration for the feelings of the trumpet player. The mechanisms causing dizziness appear obvious, but it seemed worth while to obtain continuous records of the pressures blown and their consequent circulatory effects, since observation suggested that greater pressures across the vibrating aperture were needed in trumpet playing than in any other commonly used instrument.

Material and Methods

The measurements were made on one of us (M. F.), who is a professional player and teacher of the trumpet. Some measurements were also made on two other subjects: an amateur surgical colleague, who played in the Cambridge University dance band 30 years ago, and a novice member of the department who purports to be learning the oboe. Pressures were measured with capacitance manometers, mouth pressure with a fine water-filled "polythene" tube, and intrathoracic pressure in the oesophagus (Dornhorst and Leathart, 1952). The trumpet was held and played with the right hand, while arterial pressure was recorded in the left brachial artery.

Results

As expected, the circulatory effects of trumpet playing are similar to the effects of the Valsalva manœuvre. Fig. 1 shows the professional playing Concert A moderately loudly for 17 seconds. The pressure blown is about 80 mm. Hg, or a good deal higher than the 50 mm. Hg normally used to test the circulation (Sharpey-Schafer, 1955). The subject maintains a relatively constant pressure in producing his note, yet very few normal subjects are capable of blowing a mercury manometer to this height and maintaining it at a constant level without extensive practice. The effects on the circulation are those of a formidable Valsalva manœuvre: peripheral venous valves shut and blood accumulates distal to them. The effective cardiac-filling pressure, stroke output, and mean arterial pressure fall off rapidly. After about 7 seconds the slight rise of arterial pressure indicates the onset of reflex constriction, which persists, after cessation of blowing, during the overshoot. Since the brain is not protected by venous valves the supply pressure across it falls so that the cerebral blood flow may become inadequate during the period of blowing. More usually dizziness or black-out is maximal immediately on release of intrathoracic pressure, as occurred on the occasion of recording Fig. 1.

In Fig. 2 the professional is shown blowing a loud arpeggio up to high D. On the top note he reached a pressure of 160 mm. Hg. Thereafter he blew a series of rapid blasts which produced rapid transients on the arterial pressure curve. In Fig. 3 he is playing a long phrase from Wagner at a relatively low pressure; circulatory changes are still conspicuous. It is interesting to compare the performance of the amateur and the novice with that achieved by the professional.

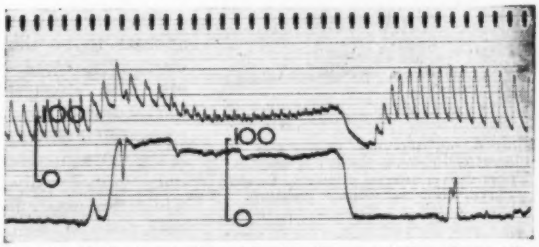


FIG. 1.—Professional player blowing Concert A for 17 seconds. Upper curve, arterial pressure. Lower curve, mouth pressure. Calibration in mm. Hg and time marker in seconds in this and subsequent figures.

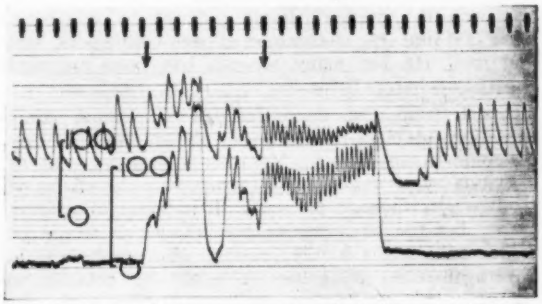


FIG. 2.—At the first arrow an arpeggio is blown to high D (160 mm. Hg mouth pressure). At the second arrow a series of rapid blasts are blown for 6 seconds.

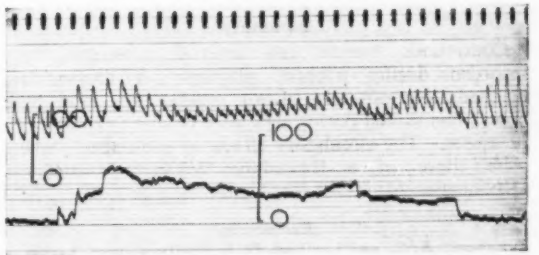


FIG. 3.—A long (28 seconds) phrase is played from *Tannhäuser* without drawing breath.

The amateur was capable of maintaining a note for nearly as long as the professional at 75 mm. Hg. When asked to blow an arpeggio he reached high C but only 110 mm. Hg mouth pressure. The volume of sound produced was less. The maximum pressure produced by the novice was 60 mm. Hg for any recognizable note.

Teachers of musical instruments or singing have curious ideas of anatomy and physiology, and they are apt to spur on their pupils with quite erroneous views on how air is expelled from the chest. It is possible, however, that they achieve success by persuading the pupil to produce uninhibited effort, for when the professional was asked to blow a mercury manometer, an instrument with which he was unacquainted, he could only achieve 80 mm. Hg. On the other hand, the novice, who could blow a trumpet only to 60 mm. Hg, easily blew the mercury to 160 mm., for he had many years' practice at this procedure (Fig. 4). These results suggest that it might be useful to record mouth or intrathoracic pressures during training in order to demonstrate errors in technique.

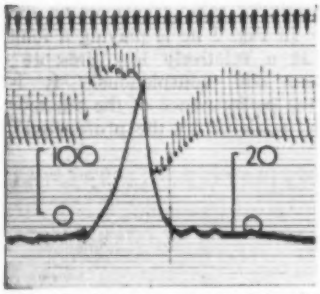


FIG. 4.—A mercury manometer is blown to 160 mm. Hg for 6 seconds. Upper curve, arterial pressure. Lower curve, forearm venous pressure.

The trumpet appears to be the instrument requiring the highest intrathoracic pressures. Oboe players reach 60 mm. Hg only occasionally, while the amateur recorded 40 mm. Hg mouth pressure when playing loud high notes on the French horn. Although trumpet playing produces high intrathoracic pressures compared with other instruments and normal straining, it still does not approach the pressure levels induced by coughing. Over 200 mm. Hg is common in well-built males, and 450 mm. Hg for many seconds has been recorded (Sharpey-Schafer, 1953).

Apart from the discomfort of occasional dizzy sensations or black-outs, trumpet players are not likely to come to any harm. Vasodilatation from heat or previous hyperventilation will exaggerate the effects of a given intrathoracic pressure. It is better to sit than stand, but the strict supine posture, which would be better still, seems hardly feasible. For orchestras in severe financial difficulties it might be possible to dispense with the assistant or "mate" if the trumpeter wore a pilot's pressure-suit, which could be surreptitiously inflated by a switch on the conductor's desk.

Summary

Continuous mouth and arterial pressures were recorded during trumpet playing. A professional reached 160 mm. Hg blown pressure on loud high notes; less skilled performers were unable to reach such pressures. The circulatory effects of prolonged playing were those of a formidable Valsalva manœuvre. Dizziness or black-out may result.

REFERENCES

Dornhorst, A. C., and Leathart, G. L. (1952). *Lancet*, **2**, 109.
Sharpey-Schafer, E. P. (1953). *Brit. med. J.*, **2**, 860.
—— (1955). Ibid., **1**, 693.

ON RUBELLA IN PREGNANCY

BY

JULIA BELL, M.A., F.R.C.P.

From the Galton Laboratory, University College

In the fifth James Mackenzie Lecture Dr. G. F. Abercrombie (1959) described the following sequence of events experienced by a patient who had sought his advice: "A lady, 14 weeks pregnant, and her 4-year-old daughter, simultaneously developed german measles. The mother knew all there was to be known at that time about pregnancy and german measles, and I immediately obtained confirmation of the diagnosis from a dermatologist. Thence to an obstetrician who, though clearly in favour of terminating the pregnancy, asked that his opinion be confirmed by a colleague. The second was just as hesitant as the first, and I had finally to take her to a physician before the operation could be done. This physician simply said, 'You can't do anything else.'" Yes, indeed; by this time, having been to five doctors, none of whom could reassure her or allay her fears, there could be no alternative, for psychological reasons if for no others.

Dr. Abercrombie does not state when he saw this patient. If it was as far back as 1940–5 the doubt and hesitation on the part of her advisers was understandable, and even commendable, but to publish such an account to-day, as if such conduct of a case may still be excusable, seems to me to be unfortunate and possibly to invite the recurrence of doubt and hesitancy on the part of other practitioners presented with the problem.

Suggestions for the G.P.

Having considered this problem in some detail, I think that, though no definite calculation of the risks involved is yet possible, we are able to suggest certain rules for the guidance of the practitioner until more exact facts can be given, so that he should no longer have to consult colleagues who really know no more on the subject than he does; for though Dr. Abercrombie apparently scorns statisticians and refuses to take notice of percentages, in such a problem only statistics can give the help needed. He is right, however, to be cautious in accepting a simple percentage as a guide without careful consideration of the material on which it is based, on the numbers concerned, and on the snags involved, which may differ from one sample of material to another and which do make this particular problem a very elusive one.

Now the facts of the situation have accumulated so that one can state without doubt that rubella in the early weeks of pregnancy is such a menace to the normal development of the foetus that it constitutes a risk one cannot allow to be taken for the unborn child. Abortion has become the generally recognized treatment in such a case; to such an extent has this become routine treatment that maybe we can no longer hope to get a measure of the risk involved or discover what proportion of such occurrences can be expected to result in a normally developed child. The important question we have to decide is at what stage of pregnancy the occurrence of rubella constitutes no menace to the child, or so small a risk that routine abortion can no longer be justified. I would, in the present state of our knowledge, suggest 12 weeks as the limiting time; a patient coming

up for advice with a history of rubella after this date should be reassured and abortion should no longer be prescribed as a routine measure and should be permitted only if the nature of the individual case required it.

I have collected from the literature accounts of 712 cases of rubella during pregnancy giving, not percentages of resulting defect, but histories of each experience, with a report on the condition of the child. Such material is, for the most part, highly selected by one factor or another which is likely to differ from one source of material to another, so that any conclusions drawn from it are not of general application and should be drawn—and received—with great caution. However, I think the summary given in the accompanying Table is of great interest and may provide pointers to those who have to make decisions in such cases.

It will be seen from the Table that cataract was noted in 149 cases, deafness in 263, and congenital heart disease in 210. In addition, 70 children were reported to show defects other than the three characteristic ones, which either were absent or the child died before they could be discovered. Of these, 36 were either stillborn or miscarried, or abortion had been produced; defects in the remaining 34 were varied and probably unrelated to the occurrence of the maternal rubella.

A further 221 children of the series were believed to be normal at the time of observation; 94 of them had a history of maternal rubella before or at the twelfth week of pregnancy, and 59 of these were known to be over the age of 2 years at the time of observation.

Sources of Information

And now a word about this material, which in the main is derived from four chief sources.

1. *Information collected from maternity hospitals at the time of birth or shortly after, rubella having been said to occur during pregnancy.*—If cataract has resulted, with or without the frequently associated microphthalmia, this anomaly would be evident; congenital heart disease might be diagnosed, but I suspect that in many cases the diagnosis might be reversed if the infant were seen again at a later date; the third characteristic defect—namely, deafness—would not be revealed at this age. Thus the only reliable information so provided concerns cataract, which would be unlikely to escape recognition whatever the source, and 149 examples of the defect in the records of 712 cases probably provide a maximum incidence.

2. *Information obtained by questionaries to parents of school entrants at the age of 6 years.*—This material is selective in that all the children who died before the age of 6 years or who were too handicapped by their defects to attend the ordinary schools are excluded from the records, and thus the figures are heavily weighted in favour of normal children, but they do provide evidence of the fact that rubella, even in early pregnancy, does not necessarily result in a defective child. There must, I think, be some doubt whether the mother of a child aged 6 can remember the week of pregnancy in which she developed rubella so long ago.

3. *Information obtained by routine inquiry in special hospitals for the deaf, for eye diseases, or for congenital heart disease.*—This information is selective in that every child is defective: no normally developed child appears in the records, and thus the figures of defect are heavily overweighted. This is particularly marked in respect of information from schools or institutions for the deaf, and must contribute largely to the excess of cases of deafness amongst the records; but the material is valuable in that the child under observation has reached an age at which all the three characteristic defects would be clearly developed if present. The doubts one may feel with regard to my large numbers for deafness alone in the population concerned bring up the question whether the deafness in so large a proportion of the cases, though associated with a history of maternal rubella during pregnancy, is in fact always causally related to it. That in so many of these cases the maternal affection had occurred in the first three months of pregnancy does suggest a causal relationship, but we should view with some doubt the aetiology of the relatively few cases noted in the later categories. It is of interest that relatively few examples of deafness in this series are associated with cataract or suspected heart disease; which again leads to the suggestion that perhaps the amount of deafness revealed in the material concerning very young children has been underestimated and that doubtless more of this defect would become evident if these cases were reviewed at a later date.

4. *Other sources of information.*—These include reports of cases in medical journals and questionaries circulated—for example, to doctors or to women who have had rubella during pregnancy. None of these are free from selection, but all tend to exaggerate the risk involved and to minimize the numbers of normally developed children in the population concerned. A routine investigation being carried out by Dr. Pitt in Melbourne and one by Professor Bradford Hill in this country should lead to unselected samples of material in the years ahead, referring to cases in which abortion has not been induced.

Summary of Defects Occurring in 712 Cases of Rubella during Pregnancy

Defect Noted in Child	Week of Pregnancy in which Rubella Occurred												Total
	1–4		5–8		9–12		12–16		>16		?		
	a	b	a	b	a	b	a	b	a	b	a	b	
Cataract only	9	7	8	1	—	2	—	—	—	3	—	—	30
,, and heart anomaly	27	8	18	18	3	4	—	—	—	—	—	—	78
,, ,, deafness	2	3	1	3	—	1	—	—	—	—	—	1	11
,, heart anomaly, and deafness	4	10	5	10	1	—	—	—	—	—	—	—	30
Deafness only	1	13	1	74	—	62	—	14	—	4	—	1	170
,, and heart anomaly	—	9	1	20	2	14	1	3	—	—	—	2	52
Congenital heart disease only	4	6	4	11	6	5	2	5	2	5	—	—	50
Total	47	56	38	137	12	88	3	22	2	12	—	4	421

a = Children observed under the age of 2 years. b = Children observed aged 2 years and over.

This report, then, can be regarded as an interim account only, based on the examination of some 100 published papers on the subject. A further and more detailed investigation is in progress.

REFERENCE

Abercrombie, G. F. (1959). *J. Coll. gen. Pract.*, 2, 11.

DEAF OR DEAD?

A CASE OF SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN AND NEOMYCIN

BY

C. W. H. HAVARD, B.M., M.R.C.P.

LAWRENCE P. GARROD, M.D., F.R.C.P.

AND

PAMELA M. WATERWORTH, F.I.M.L.T.

From the Departments of Medicine and Pathology, St. Bartholomew's Hospital, London

The following is the history of a patient who had to be warned that the treatment necessary to save his life would probably cause severe deafness. He accepted this consequence, and suffered it, but he is alive and well nearly a year later. The history also illustrates the value of tests of combined antibiotic bactericidal action in difficult cases of bacterial endocarditis.

Case Report

A police inspector aged 47 was admitted to St. Bartholomew's Hospital on February 8, 1958, complaining of not having felt well since December 4, 1957, when his urethral stricture (dating from 1946) had been dilated in this hospital. For several weeks past he had suffered from fever and night sweats, and for several days had noticed increasing lethargy and debility.

Physical examination revealed a well-built man (205 lb.—93 kg.) who was febrile (100° F.—37.8° C.) and obviously ill. There was no clinical cardiac enlargement, but examination of the heart showed evidence of a severe degree of aortic incompetence. The pulse frequency was 90 a minute and the pulse wave collapsing. The blood pressure was 130/50; a grade IV aortic diastolic murmur was conducted down the left border of the sternum, and the musical character of this murmur suggested rupture of an aortic cusp. A number of subungual splinter haemorrhages were visible, but there was no finger-clubbing and the spleen was not palpable. The urine contained no abnormal constituent, and microscopy of a centrifuged deposit revealed a few white and red blood cells only. The E.S.R. was 76 mm. in one hour (Westergren); the haemoglobin was 11 g./100 ml., the white blood count was normal, and the blood urea was 22 mg./100 ml. An E.C.G. and a chest *x*-ray examination were normal.

Bacteriological Findings.—A blood culture on the day of admission grew *Streptococcus faecalis*. This organism had a normal degree of sensitivity to penicillin (inhibition by 4 units/ml.) and to other antibiotics except tetracycline and streptomycin; the minimum inhibitory concentration of streptomycin was 50,000 μg./ml. (It was later verified that the *Str. faecalis* in his faeces was also highly resistant to streptomycin.) Tests of combined bactericidal action by the method of Martin, Sureau, and Chabbert (1952) showed that no combination of penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, vancomycin, or bacitracin, or any of these singly, completely sterilized the inoculum. A further experiment was done in which serial viable counts were made by an accurate method, using the more promising six antibiotics or combinations in a concentration of 10 μg./ml. (penicillin 10 units/ml.), whether alone or in combination. The following were the mortalities after 24 hours: penicillin, 99.75%; erythromycin, 51%; vancomycin, 69%; penicillin + erythromycin, 60%; penicillin + vancomycin, 81%; Penicillin + streptomycin, 99.85%.

From this it appeared that penicillin alone was as effective as anything else, and treatment, which from February 10 had consisted of penicillin, 1 mega unit six-hourly, and streptomycin, 1 g. b.i.d., was continued from February 14 with penicillin only (2.5 mega units six-hourly) supplemented by probenecid, 0.5 g. q.d.s. This regime was continued for six weeks.

After four days the patient became and remained afebrile. His immediate progress was uneventful. The E.S.R. had fallen to 20 mm. in one hour by the end of the sixth week, and he not only felt restored to complete health but had gained 2.3 kg. in weight. The musical character of the aortic diastolic murmur had gradually disappeared, and the diagnosis of subacute bacterial endocarditis on a bicuspid aortic valve with rupture of one of the cusps seemed to be beyond dispute. No signs of relapse appeared over a further week of observation, and he was discharged from hospital on April 2.

Relapse

Two weeks after leaving hospital he complained of dysuria, and a few days later the night sweats and lethargy returned. On April 26 he was readmitted to hospital. He was febrile (101° F.—38.3° C.) and obviously ill, but the physical signs were essentially unchanged. The blood pressure was 130/50 mm. Hg and there was a definite though slight increase in the heart size. Microscopy of the urine revealed an excess of leucocytes and a few red blood cells; culture was sterile. The E.S.R. was 60 mm. in one hour, the haemoglobin was 8.9 g./100 ml., and the white blood count 7,200/c.mm., with a normal differential count. The blood urea was 23 mg./100 ml. and the urine concentration and dilution tests were normal.

Bacteriological Findings.—Blood cultures made on April 26 and 27 yielded a profuse growth of *Str. faecalis* (187 and 190 colonies per ml. in pour plates). This organism and that isolated originally were sent to Dr. S. D. Elliott, who kindly reported that they were identical, belonging to his type D 15, which is the type 9 of Sharpe and Shattock (1952). It was still inhibited by 4 units of penicillin per ml., but killed by penicillin much more slowly. The only remaining resource appeared to be neomycin. Although the organism grew in 10 μg. of this antibiotic per ml. (the minimum inhibitory concentration was 16 μg./ml.), either 5 or 10 μg. of neomycin per ml. combined with 10 units of penicillin per ml. proved to be completely bactericidal. This was the only combination found to sterilize the inoculum (of about 10^6 streptococci per ml.) in all the tests made.

Treatment with penicillin, 2½ mega units six-hourly, streptomycin, 1 g. daily, and probenecid, 0.5 g. t.i.d. was started on April 28. By May 6 the full laboratory findings were available, and intramuscular neomycin, 0.5 g. eight-hourly, replaced the streptomycin and probenecid, the patient's consent having been obtained for the use of a drug which would probably make him deaf. He became and remained afebrile after five days' treatment.

Assays of the antibiotics in four specimens of blood on May 7 and 8 showed a penicillin content varying from 23 to 5 units/ml. and of neomycin from 32 to 8 μg./ml. according to the interval since the last dose.

After 10 days' treatment with neomycin granular casts were noticed on microscopy of the urine, and after two weeks albumin was detected on routine testing. By the end of 34 days the blood urea had risen to 63 mg./100 ml. However, this was transient, and within one month of discontinuing the neomycin the blood urea had fallen to 40 mg./100 ml. and there were no casts on microscopy of the urine.

The first symptoms of deafness appeared on the 28th day of neomycin treatment: these symptoms became more severe. Neomycin therapy was discontinued on the 35th day. Nevertheless the deafness progressed, and by August 8 (60 days after the beginning of neomycin therapy) audiograms revealed a total loss of cochlear function.

Neomycin was discontinued on June 9. The patient was discharged from hospital two weeks later and has remained well. His deafness is complete, but there are no symptoms referable to the cardiovascular system, and the heart size has remained unchanged over the last six months.

Discussion

It is generally accepted that bactericidal antibiotics are needed for the treatment of subacute bacterial endocarditis. In this case the bactericidally synergic combination of penicillin and streptomycin, which is usually successful in the treatment of *Str. faecalis* endocarditis (Hunter, 1946; Cates, Christie, and Garrod, 1951; Robbins and Tompsett, 1951), was inapplicable owing to the high degree of resistance of the organism to streptomycin. The less complete bactericidal action of penicillin proved inadequate. The alternative combination of penicillin and neomycin proved to be completely bactericidal, and the clinical result justified the confidence placed in it. It is possible that a shorter course might have effected a cure, with less or no damage to hearing, but when a patient has relapsed after one long and apparently successful course, there is natural reluctance to curtail another.

A minor feature of interest in this case is the origin of the infection. *Str. faecalis* endocarditis occurs in young women as a complication of septic abortion and in older men as a consequence of infection of the urinary tract. In this patient, dilatation of a urethral stricture precipitated it, as in Case 1 of the series described by Robbins and Tompsett (1951). This is evidently a hazardous procedure in men with heart valves predisposed to infection, and, should it have to be repeated in our patient, protection with a bactericidal antibiotic, possibly vancomycin in preference to further neomycin, will have to be provided.

Summary

Infection of the aortic valve following dilatation of a urethral stricture in a man aged 47 was caused by a strain of *Str. faecalis* highly resistant to streptomycin, although of normal sensitivity to other antibiotics except tetracycline. A long course of penicillin in large doses was followed by relapse.

Only a mixture of penicillin with neomycin was found to be completely bactericidal for this organism. These antibiotics were accordingly given, and the patient was alive and well seven months later, but totally deaf.

We are indebted to Dr. A. W. Spence, under whose care the patient was treated, for permission to publish this case.

REFERENCES

Cates, J. E., Christie, R. V., and Garrod, L. P. (1951). *Brit. med. J.*, **1**, 653.

Hunter, T. H. (1946). *Amer. J. Med.*, **1**, 83.

Martin, R., Sureau, B., and Chabbert, Y. (1952). *Bull. Soc. méd. Hôp. Paris*, **68**, 1192.

Robbins, W. C., and Tompsett, R. (1951). *Amer. J. Med.*, **10**, 278.

Sharpe, M. Elisabeth, and Shattock, P. M. Frances (1952). *J. gen. Microbiol.*, **6**, 150.

RECURRENT PHLYCTENULAR KERATO-CONJUNCTIVITIS TREATED BY DESENSITIZATION TO TUBERCULIN

BY

ARNOLD PINES, M.D., M.R.C.P.Ed.

Department of Tuberculosis and Diseases of the Respiratory System, Edinburgh University

Though usually a benign and transient phenomenon, phlyctenular conjunctivitis can be distressing and disabling, particularly when the cornea is involved. In mild cases local treatment may suffice, but it often fails when there are more severe manifestations. Since phlyctenules are allergic phenomena, most often to tuberculo-protein, the antituberculous drugs have often been given in treatment with apparent success. In the case described below they had no effect, and more fundamental treatment had to be undertaken.

Case Report

A boy aged 11 was seen in March, 1957. Since the age of 6 he had had four or five attacks of phlyctenular kerato-conjunctivitis a year. These attacks had been distressing and he had lost several months of attendance at school each year. Treatment had always been on general lines, and he had never been given antituberculous chemotherapy. Both eyes had been equally affected, and small scars had remained in each cornea at the centre and at the limbus, though these had not affected vision. In the most recent attack a phlyctenule had appeared in each eye, and there were moderate blepharospasm and photophobia and also some general disturbance. No lesions of the retina or choroid were present. A radiograph of the chest showed a very large calcified paratracheal gland and two small calcified lesions in the right upper lobe; a radiograph taken in 1952 had shown identical changes. A Mantoux test in 1955 had been positive to 0.1 T.U. (1:100,000); this was repeated in 1957 in the same dilution, and was again positive, the induration measuring 10 by 8 mm.

The presence of these calcified tuberculous pulmonary lesions and the marked sensitivity to tuberculin indicated that the phlyctenular kerato-conjunctivitis was an allergic response to tuberculo-protein. The patient was admitted to hospital for a trial of chemotherapy and was given *para*-aminosalicylic acid (P.A.S.), 5 g., and isoniazid, 100 mg., twice daily from March 21. Cortisone eyedrops were given daily. Both phlyctenules gradually subsided, but after five weeks the right phlyctenule reappeared, accompanied by blepharospasm and photophobia, though chemotherapy was still being given.

Tuberculo-protein is present in the bodies even of dead bacilli, and therefore it was thought that further chemotherapy by itself might well be ineffective. It was rational to abolish the allergic state by desensitization to the offending allergen, tuberculo-protein. The phlyctenules had recurred so often over five years and the patient's life had been disturbed so much that it was reasonable to attempt the rather prolonged treatment needed.

In severe allergic states desensitization may be greatly eased and speeded by a cover of corticosteroids (Pines, 1957). The patient was therefore given prednisolone, 5 mg. three times daily, while P.A.S. and isoniazid were continued to guard against the very remote possibility of reactivation of the pulmonary tuberculosis. 0.1 ml. of old tuberculin, 1:100,000 dilution, was given intramuscularly without reaction; afterwards the dose was approximately doubled daily without incident. On the twelfth day he had a slight headache, fever, and vomiting with 1 ml. of old tuberculin, 1:1,000. The prednisolone was increased to 5 mg. four times daily and desensitization was continued. A mild reaction followed the injection of 0.75 ml. of old tuberculin

1 : 100, but there was none with 0.4 ml. The dose was then increased by 0.1 to 0.2 ml. daily, but a further reaction occurred with 0.4 ml. of pure old tuberculin. 0.1 ml. of the same strength was given without incident and the dose was increased by 0.05 ml. daily.

After seven weeks 1 ml. of old tuberculin was given without incident, and this was continued daily while the prednisolone was gradually withdrawn over the next two weeks. The injections of pure tuberculin gave no reaction intramuscularly or intradermally when the prednisolone was withdrawn, and he was discharged 10 weeks after desensitization had begun. P.A.S. and isoniazid were discontinued soon after. During the whole course of treatment no fresh phlyctenules appeared.

To maintain the desensitized state, 1 ml. of pure old tuberculin was given intramuscularly each week. It was intended to continue the tuberculin injections for a year, to ensure that no phlyctenules recurred. In April, 1958, the patient had to be admitted to another hospital after breaking his ankle, and inadvertently no further injections were given. When he was seen in May, he was well and tuberculin injections were not started again. He had had 1 ml. weekly for nine months. He was seen again in November, 1958, and remained well. A Heaf test at this time showed slight return of sensitivity to tuberculin (grade 1). There had been no attack of phlyctenular kerato-conjunctivitis for one and a half years since April, 1957. Before treatment there had usually been seven or eight attacks during a similar period of time.

Discussion

The treatment of severe and recurrent phlyctenular kerato-conjunctivitis has usually been on empirical lines. Most authorities recommend general hygienic and nutritive measures. Antituberculous chemotherapy has been said to be curative (Woods, 1951 ; Arruda, 1953). It certainly had no effect alone in the above case ; further, the hypersensitivity which is responsible for phlyctenular kerato-conjunctivitis may persist even when only dead tubercle bacilli remain. Local treatment with cortisone has a palliative value but does not prevent further attacks. Courses of tuberculin have been recommended (Duke-Elder, 1938), and desensitization has sometimes been attempted (Woods, 1949, 1951).

In the above case it was rational to desensitize to the offending allergen, tuberculo-protein. Probably the prednisolone which was also given depressed tuberculin sensitivity and allowed the patient to be desensitized quickly and easily. There were several reactions to tuberculin during treatment, so that it is unlikely that systemic corticosteroids given alone would have prevented further attacks of kerato-conjunctivitis, while they could have suppressed tuberculin sensitivity only temporarily. It is possible that the attacks may have ceased spontaneously. but this seems very unlikely, given the five years of frequent recurrences, with the appearance of three fresh phlyctenules shortly before desensitization was begun.

Desensitization to tuberculin can be recommended only in patients with severe and recurrent phlyctenules. The treatment usually takes at least several weeks, and reactions can be unpleasant or even dangerous, particularly in inexperienced hands. In mild cases there may be only few recurrences or complications and local treatment is sufficient. In the above case there were frequent recurrences over five years and much disturbance of normal life. These justified the 10 weeks in hospital that were needed to obtain what appears to be permanent cure.

Summary

A boy aged 11 had had more than 20 attacks of phlyctenular kerato-conjunctivitis. These were manifestations of hypersensitivity to tuberculo-protein, because there were calcified tuberculous pulmonary lesions and the tuberculin test was positive to O.T. 0.1 unit (1 : 100,000). Local and general treatment, and also antituberculous drugs, had not prevented recurrences. He was slowly desensitized to tuberculin under a cover of prednisolone, and 1 ml. of tuberculin was given weekly for nine months to maintain the desensitized state. No phlyctenules have appeared since treatment started and for the nine months since it was stopped.

I thank Professor J. W. Crofton, Professor G. I. Scott, and the late Dr. N. Pines for their advice and criticism.

REFERENCES

Arruda, J. de (1953). *Rev. bras. Oftal.*, **12**, 83.
Duke-Elder, W. S. (1938). In *Textbook of Ophthalmology*, 2, 1695. Kimpton, London.
Pines, A. (1957). *Brit. med. J.*, **2**, 202.
Woods, A. C. (1949). *Brit. J. Ophthal.*, **33**, 197.
—— (1951). In *Systemic Ophthalmology*, edited by A. Sorsby, pp. 155, 185. Butterworth, London.

MONILIAL GRANULOMA

BY

K. NITYANANDA, M.B., B.S., D.B.

Department of Mycology, Medical Research Institute, Colombo, Ceylon

This report deals with a case of monilial granuloma, a severe therapy-resistant mycotic infection, due to *Candida albicans*. The mycological and histopathological findings are also discussed.

Case Report

A 5-year-old girl was seen in May, 1957, with growths on the scalp which had first been noticed towards the end of April, 1957. During the preceding eight months she had been treated for malnutrition and oral thrush at a children's hospital. Her history, and that of her family, could not be elicited.

Examination showed a malnourished pale child. The anterior two-thirds of the scalp (Fig. 1) was covered with thick, hard, greyish-yellow crusts, which when removed revealed a granulating, freely bleeding base. The crusts were round, concave, and saucer-like, and adhered fairly closely to the skin, and here and there they were pierced by single hairs. The eruption on the scalp was diagnosed as staphylococcal impetigo, favus, and chronic lupoid sycosis prior to the receipt of the microscopical and cultural findings. Lesions without crusts were seen on the neck, shoulders, and upper part of the back and chest. The commissures of the mouth were fissured and the mucous membrane was covered with a thick greyish-white exudate. The nail of the left middle finger was affected.

On December 11, 1956, she was Mantoux positive—6 mm. *X*-ray examination of the chest on March 7 and August 17, 1957, and on May 9, 1958, showed no abnormalities.

Mycological Findings.—Potassium hydroxide preparation of scrapings taken from the scalp and neck lesions revealed a tremendous amount of fine, straight, poorly refractile hyphae. There were also larger circular bodies with thick walls, obviously chlamydospores, which were attached to short curved hyphae (Fig. 2). The hair, under potassium hydroxide, contained no hyphae, spores, or air bubbles. The preparations from the mouth contained a considerable number of interwoven filaments. Culture on Sabouraud's dextrose agar yielded a growth of flat, smooth, whitish

colonies with a yeasty odour. Fungus did not grow from hair which was cleared of all crusts. Slide cultures using corn-meal agar showed a great number of chlamydospores. The organism fermented glucose and maltose with the formation of acid and gas, and lactose with the formation of acid only; it did not ferment sucrose.

Histological Examination.—Macroscopic examination showed a nodular papilloma with cornification of the surface. Microscopically the surface consisted of laminated wavy cornified material, and cells were found immediately under this cornifying surface. The Malpighian layer was thickened and was seen to pass down in large blunt growths. Normal-looking hairs and hair follicles were seen passing through. Areas of necrosis were present, mostly round hair follicles. The Hotchkiss-MacManus stain revealed a great many mycelia throughout the section (Fig. 3).

FIG. 1.—Photograph showing anterior two-thirds of scalp covered with crusts.

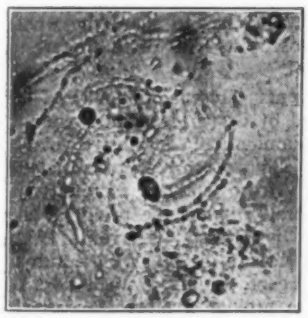


FIG. 2.—Section showing poorly refractile hyphae and large circular bodies, obviously chlamydospores. Potassium hydroxide preparation.

FIG. 3.—Section of the crust, showing an abundance of mycelia.

Pathogenicity. — A saline suspension of the organism was injected into the ear vein of a rabbit. The animal died after six days, and at necropsy the kidneys were swollen and studded with abscesses, from which organisms were recovered. It was therefore concluded that the eruption was due to infection by *C. albicans*. These findings were confirmed by Dr. R. W. Riddell, Institute of Dermatology, London, and Dr. J. Walker, Mycology Reference Laboratory, London.

Comment

Monilial granuloma caused by *C. albicans* is a rare specific entity. The case reported by Hauser and Rothman (1950) was strikingly similar to the present case. Their review of all available earlier literature on the subject referred to only 13 other related cases. Another case of generalized moniliasis was reported at a meeting of the Minnesota Dermatological Society (1953). Analysis of all these 16 cases showed that the age of onset was always in early childhood. In six cases the eruption appeared during the first year of life, in the remainder before the fifth year. The sexes were equally susceptible to infection. Of the earlier 15 patients, 14 were white and one a negro. The primary site of infection was the oral mucous membrane in seven cases, the scalp or face in six. In two cases the original site was not reported. In the case under review it was evident that the infection started in the mouth.

In all biopsies of the granuloma it was found that there was a tremendous proliferation of the organism in the infected site, in contrast to the common types of moniliasis, in which it was often difficult to demonstrate the organism in direct preparations.

REFERENCES

Hauser, F. V., and Rothman, S. (1950). *Arch. Derm. Syph. (Chicago)*, **61**, 297.

Minnesota Dermatological Society (1953). *A.M.A. Arch. Derm. Syph.*, **68**, 105.

STENOSING TENOSYNOVITIS OF THE COMMON PERONEAL TENDON SHEATH

BY

D. R. GUNN, M.Ch.Orth., F.R.C.S.Ed.

Senior Lecturer in Orthopaedic Surgery, University of Malaya, Singapore

In view of the rarity of stenosing tenosynovitis of the common peroneal tendon sheath it is thought worth while to record the following case. Two previous cases were reported by Parvin and Ford (1956).

Case Report

The patient, a female Eurasian aged 45, was employed as a nurse. She complained of pain and swelling of the left ankle which had persisted for three months. The pain was felt only when she was walking; she could still stand without discomfort. The onset had been gradual and no injury had occurred.

On examination her general condition was good. She had a tender swelling below and behind the external malleolus of the left ankle in the line of the peroneal tendons. There was a full range of movement at the ankle and mid-tarsal joints, and pain was produced only on maximum inversion; the location of the pain was just behind the tip of the external malleolus.

Investigations.—White blood cells, 7,800 per c.mm. (polymorphs 69%, lymphocytes 26%, neutrophils 2%, eosinophils 3%); haemoglobin, 85%; total red cells, 4,200,000. Urine, nothing abnormal on routine examination. E.S.R., 9 mm. in first hour. Chest *x*-ray film was within normal limits and ankle film was normal.

It was considered clinically that the condition closely resembled the common stenosing tenosynovitis at the wrist and it was decided to make an exploration.

Operation.—This was performed on January 11, 1957, under general anaesthesia, and a tourniquet was used. An incision 3 in. (7.5 cm.) long was made in the line of the peroneal tendons from behind the external malleolus to below and just in front of it. It was immediately obvious that the inferior peroneal retinaculum was grossly thickened. A little further investigation showed a marked swelling of the tendon of peroneus brevis, just proximal to the retinaculum; the tendon sheath was thickened and lined with a velvety brown tissue (Fig. 1). The tendon of peroneus

longus appeared to be normal. A large piece of the thickened inferior retinaculum was excised, and this immediately allowed the tendon to move more easily (Fig. 2). No abnormality of the tendons, as is often seen in tendovaginitis at the wrist, was present. The skin was

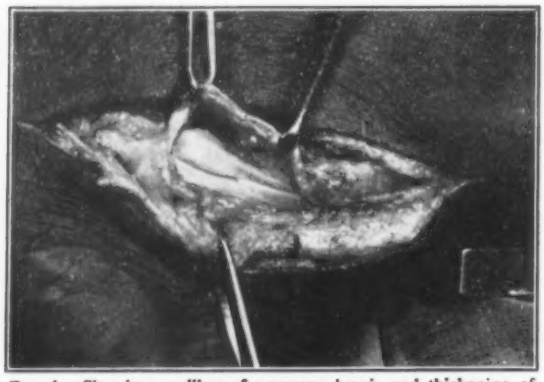


FIG. 1.—Showing swelling of peroneus brevis and thickening of retinaculum.

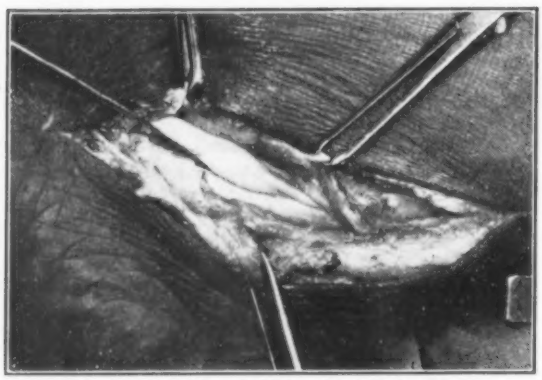


FIG. 2.—After excision of thickened area of retinaculum.

sutured and a firm dressing applied. The biopsy report stated: "Chronic inflammatory tissue with no evidence of tuberculosis."

The operation gave complete relief of pain, and the swelling subsided.

Comment

Diagnosis of this condition is not difficult to make if the possibility of its occurrence is remembered.

The operation produced as satisfactory a result in the ankle as it does in the wrist.

REFERENCE

Parvin, R. W., and Ford, L. T. (1956). *J. Bone Jt Surg.*, **38A**, 1352.

In the preface to the eleventh edition of his *Clinical Examination of the Nervous System* Professor G. H. Monrad-Krohn writes that it will probably be the last from his hand. He retired recently from the chair of neurology in the University of Oslo, and the present edition of this well-known textbook has been revised with the assistance of Professor S. Revsum. Although some account of electro-encephalographic, radiographic, and other technical methods of diagnosis is included, the main emphasis of the book is on clinical examination, which the author regards as one of the chief pillars of neurology. The book is published by H. K. Lewis and Co. Ltd., London (pp. 466 +xx; illustrated. 1958. 40s.).

NITROUS OXIDE ANAESTHESIA FOR BRONCHOSCOPY

A METHOD SUITABLE FOR OUT-PATIENTS

BY

DAVID BROWN, M.B., F.F.A.R.C.S.
Senior Anaesthetic Registrar, Middlesex Hospital and London Chest Hospital

AND

J. V. I. YOUNG, M.B., F.F.A.R.C.S.
Anaesthetic Registrar, London Chest Hospital

This paper is based on our experience in giving general anaesthesia for over 700 bronchoscopic examinations, mainly on out-patients.

Bronchoscopy is a challenge for the anaesthetist. Whatever method of anaesthesia is used there is a danger of asphyxia. There are several reasons for this. The patients are often in poor general health, and in particular may suffer from a diminished pulmonary reserve, excessive sputum, hyperinflation, and obstructive airway disease, or cardiovascular insufficiency. The area of lung available for gas exchange may be reduced by occlusion or kinking of some of the more proximal air passages when the bronchoscope is passed deep into the bronchial tree. Severe bleeding after bronchial biopsy sometimes floods the airway. The anaesthetist has to share the whole airway with the bronchoscopist, who often prefers to work in a darkened room.

Most anaesthetic agents present difficulties. If anaesthesia is maintained by drugs given intravenously the effects outlast the examination. Explosive volatile agents are not safe. Chloroform, halothane, and trichlorethylene, apart from other factors, are objectionable to the operator unless the proximal end of the bronchoscope is closed (Herron, 1950; Mathewson *et al.*, 1956; Kovacs, 1957). We use nitrous oxide as our principal agent, adding a small dose of thiopentone for adults to provide a more comfortable and speedy induction. As in other published methods, muscle relaxation is obtained with suxamethonium (Churchill-Davidson, 1953; Kelsall, 1954; Cheatle and Chambers, 1955; Buck, 1955; Green and Coleman, 1955; Pinkerton, 1957).

Preliminary Assessment of Patient

The case histories and chest radiographs are examined. Superior vena caval obstruction is regarded as an absolute contraindication because the action of drugs given intravenously is apt to be delayed, and abolition of the negative inspiratory intrathoracic pressure increases the venous congestion. Cardio-vascular disease is a relative contraindication: each patient is assessed individually. We have preferred topical analgesia for two patients with coronary artery insufficiency and for three patients who had cerebral vascular disease. Including five patients with mediastinal venous obstruction, our rejection rate for this type of general anaesthesia has been about 2%.

A simple explanation of the procedure is given to each patient. They are told that they will be in a semiconscious, dream-like state for the examination, which they will not find unpleasant. They are not told that they will go right off to sleep. The majority

remember nothing, but just occasionally a patient will hear and recall what has been said during the bronchoscopy. It is important that everyone in the team should realize this.

Technique

Adults are given 1/75 gr. (0.8 mg.) of atropine sulphate intramuscularly one hour before the examination. A Gordh needle is fixed in position in a left forearm vein. The flowmeters of the gas machine are set to deliver 5 litres of oxygen and 10 litres of nitrous oxide a minute, and the patient is asked to breathe this from a facepiece. Then 1 ml. of 2½% thiopentone solution for each two stone (0.08 ml. per kg.) of body weight is rapidly injected intravenously. To avoid the muscle fasciculation of end-plate depolarization, this solution contains about 1.5 mg. of gallamine triethiodide per ml., prepared by adding 160 mg. to a 100-ml. bottle of 2½% thiopentone solution. After this has taken effect it is followed by suxamethonium chloride, 5 mg. for each stone (0.8 mg. per kg.) of body weight.

When breathing stops the lungs are ventilated with the nitrous oxide and oxygen mixture for three minutes. This reduces the amount of nitrogen and carbon dioxide in the lungs, increases alveolar oxygen tension, and provides an effective concentration of nitrous oxide in the brain. We regard this step as the essential part of the technique. To ventilate the lungs efficiently we use an anaesthetic assembly incorporating a non-rebreathing valve.

The Negus bronchoscope is passed with the gas mixture flowing into its proximal end through tubing attached to the nipple provided. The instrument should be introduced without delay because the absorption of nitrous oxide and oxygen from the alveoli into the blood is rapid. A significant replacement of the mixture of gases in the lungs by room air can occur in a short time if the airway is clear, even if there are no respiratory movements. If delay is anticipated—for example, for teaching purposes—we pass an insufflation catheter through the larynx to within an inch (2.5 cm.) of the main carina to deliver the nitrous oxide and oxygen (Cheatle and Chambers, 1955; Buck, 1955).

Apnoea and full muscle relaxation are kept up during the bronchoscopy by intermittent doses of suxamethonium. The second dose is usually required before passing the bronchoscope. The chest is compressed rhythmically to lessen the accumulation of carbon dioxide (Toker, 1955; Green and Coleman, 1955; Bayuk, 1957). We have found that the Pinkerton (1957) cuirass is more convenient than the hands for this purpose.

Should cyanosis occur it is corrected without delay. The bronchoscope is withdrawn until its tip lies above the main carina. The nitrous oxide and oxygen mixture is passed directly down the lumen of the bronchoscope using a No. 8 Magill (32 F.C.G.) endotracheal tube and connexions (Churchill-Davidson, 1953). Additional oxygen may be added by using the bypass. Loss of gases around the side of the bronchoscope can be reduced by depressing the chin. If the hypoxia is caused by profuse haemorrhage following bronchial biopsy, suction must alternate with inflation. We keep a bronchus blocker available in case the haemorrhage is not controllable by suction.

Usually the bronchoscopy proceeds without interruption. When the examination is over, the bronchoscope is removed and the lungs are again ventilated with the nitrous oxide and oxygen mixture, using a facepiece and oropharyngeal airway until muscle power has returned. The patient is then sat up, regains unconsciousness quickly, and is encouraged to cough. Out-patients are kept resting for at least one hour.

Children have not been bronchoscoped as out-patients. They are premedicated with an intramuscular injection of papaveretum and scopolamine, to which is added atropine 1/300–1/150 gr. (0.2–0.4 mg.). For each 5 lb. of body weight 1 minim (0.06 ml.)—that is 0.026 ml. per kg.—of the standard solution containing papaveretum 1/3 gr. (20 mg.) and scopolamine 1/150 gr. (0.4 mg.) per ml. is given (Doughty, 1957). Nitrous oxide and oxygen are used to induce anaesthesia, and the intravenous needle is inserted when the child is unconscious.

Results

At the time of writing we had used this method of anaesthesia for 723 bronchoscopies. The age distribution of the patients is given in Table I. The duration of the examination has varied between 3 and 30 minutes, but usually five patients can be anaesthetized and bronchoscoped in an hour. Each patient is conscious and talking rationally before the anaesthetist starts the induction of anaesthesia on the next patient.

TABLE I

Age (years):	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90
Total No.	13	1	15	48	140	258	207	39	2
Percentage of total (approx.)	1·8	0·14	2·1	6·6	19·3	35·7	27·2	5·4	0·28

There have been no fatalities.

Complications

Before we used gallamine to stop the muscle fasciculations caused by suxamethonium severe pain in the trunk and limbs was common during the first few days following the examination (Morris and Dunn, 1957). Prolonged apnoea occurred once.

Case 1.—A man aged 61 and weighing 9 stone (57 kg.) had a two-months history of breathlessness, cough, blood-streaked sputum, and right-sided chest pain. Radiography showed a right hilar opacity with peripheral shadowing at the right apex. He was premedicated with atropine, 1/75 gr. (0.8 mg.), and given thiopentone, 112 mg., with gallamine 8 mg. This was followed by suxamethonium, 50 mg. Bronchoscopy showed a carcinoma of the right main bronchus. A biopsy was taken. Apnoea persisted for two hours. During this time his lungs were ventilated with nitrous oxide and oxygen. Three pints (1.7 litres) of 5% dextrose in water was given intravenously to help get rid of the paralysant drugs. When spontaneous respiration began it was inadequate. Atropine, 1/75 gr. (0.8 mg.), was given intravenously: after 10 minutes this was followed by neostigmine, 0.5 mg. Improvement occurred, and muscle power and respiration became adequate after a further 2 mg. of neostigmine. He had no after-effects.

Histological examination of the biopsy showed squamous-cell carcinoma, and he was admitted for further treatment. A curare-sensitivity test was performed and no objective signs were noted. For his thoracotomy, general anaesthesia was induced and maintained with nitrous oxide and oxygen.

Relaxation was obtained with the dimethyl ether of tubocurarine (total dose 24 mg.). A Carlens catheter was used to control the airway. After prolonged dissection the growth was found to be inoperable. Atropine, 1/75 gr. (0.8 mg.), with neostigmine, 2.5 mg., was given at the termination of anaesthesia. Recovery was uneventful.

The patient's serum was found to have a pseudocholinesterase level which was low (23 units).

Anticholinesterase administration was also required for another patient.

Case 2.—This patient was a diabetic man aged 43. A total dose of 450 mg. of suxamethonium was required for the bronchoscopy, which lasted 10 minutes. Partial neuromuscular block persisted after the examination, which we judged to be antidepolarizing in nature. Atropine and neostigmine administration was followed by recovery.

Discussion

It was solely out of consideration for the patients themselves that we decided to abandon topical analgesia alone as a routine for bronchoscopy. It is true that people can be bronchoscoped satisfactorily with sedation and surface analgesia only, but there is no doubt that many do suffer considerable distress. We did not regard this suffering as an unavoidable necessity: general anaesthesia might be preferable for routine use. In order to justify the change in an out-patient clinic the method used must not increase the risk for the patient, hamper the operator, give more work to the nurses, or use more hospital beds. We did not find that any of the published methods would fulfil these requirements. Some of the more recent British methods are set out in Table II for comparison. Our attempt has been satisfactory both for patients and for staff, and we consider it worth recording. Other advantages have become apparent. The surgeons have assured us that the examination is made easier and allows a better view of the less accessible parts of the bronchial tree. No sedative is included in the premedication, and surface analgesics are not used. The patients therefore have the benefit of full protective reflexes immediately after the examination.

The technique is not without its disadvantages. There are the dangers attendant upon the administration of any general anaesthetic, and there is the possibility of prolonged apnoea following suxamethonium. We would like especially to stress the importance of co-operation between surgeon, anaesthetist, and nursing staff. Very close attention should be paid to the finer points of technique.

We found 1/100 gr. (0.6 mg.) of atropine insufficient to antagonize the muscarinic effects of suxamethonium; 1/75 gr. (0.8 mg.) is more satisfactory. Sufficient narcosis is given by 12.5 mg. of thiopentone for every stone (2 mg. per kg.) of body weight. Our intention is to produce in the patient a state in which apnoea and positive-pressure ventilation are tolerated. Full surgical anaesthesia is not intended; a dose of thiopentone sufficient to do this would delay the recovery of consciousness.

Summary

A method is described of giving general anaesthesia for bronchoscopy, using nitrous oxide as the principal narcotic agent. It has been used satisfactorily in over 700 patients.

TABLE II.—*General Anaesthetic Methods for Bronchoscopy*

Author	Premedication	Induction	Relaxant	Additional Procedures	Respiration During Bronchoscopy	Maintenance	Reversal of Paralysis
Churchill-Davidson (1952)	"Omnopon" + scopolamine or "Omnopon" + atropine	250–500 mg. thiopentone	80–120 mg. gallamine	Inflation with oxygen. Lignocaine to cords, trachea, etc., followed by inflation with oxygen and TCE*	Spontaneous but weak. If cyanosis occurs, oxygen given by Magill tube inserted into bronchoscope	100–200 mg. thiopentone if necessary	Atropine 1 mg. Neostigmine 2·5 mg.
Churchill-Davidson (1953)	Papaveretum + hyoscine or Papaveretum + atropine	300–500 mg. thiopentone	50 mg. suxamethonium	Hyperventilation with oxygen. Lignocaine to cords, etc.	Complete apnoea. Oxygen via Magill tube in bronchoscope if cyanosis occurs	Additional suxamethonium as necessary. TCE in oxygen if more than 500 mg. thiopentone required to maintain sleep	
MacIntosh (1954)	Morphine + atropine	300 mg. thiopentone	80 mg. suxamethonium	Inflation with oxygen or air. 4% cocaine to pyriform fossa, cords, trachea, etc.	Spontaneous and adequate	Thiopentone as necessary	
Kelsall (1954) (a)	Papaveretum + scopolamine or	0·5–1 g. thialbarbitone	50 mg. suxamethonium	Inflation with oxygen. 1% amethocaine to cords, etc. Reinflation with oxygen	Complete apnoea. Artificial respiration by manual compression of chest	Oxygen down side tube of bronchoscope. Suxamethonium as required	
Kelsall (1954) (b)	Morphine + atropine		60–120 mg. gallamine	As above, but reinflation with oxygen + TCE	Spontaneous, but assisted if necessary	Oxygen and TCE down side tube of bronchoscope. Thiopentone + gallamine as required	Atropine. Neostigmine
Cheatle and Chambers (1955)	Papaveretum + scopolamine	Sleep dose of thiopentone	50 mg. suxamethonium	Inflation with oxygen. Insertion of "portex" tube through larynx to level of carina	Complete apnoea	Oxygen 3 l. minute through "portex" tube. Suxamethonium as required	
Buck (1955)	,,	Thiopentone	Suxamethonium	Endobronchial suction catheter through larynx to carina	,, ,,	Nitrous oxide 10 l. Oxygen 5 l./minute through catheter	
Green and Coleman (1955)	Pethidine or morphine with atropine, or scopolamine or chlorpromazine	Thiopentone, up to 500 mg.	,,	Monaghan type cuirass respirator fitted to patient. Pump turned on. Lignocaine to cords, etc.	Complete apnoea. Artificial respiration by means of cuirass	Thiopentone and suxamethonium as required	
Pinkerton (1957)	Papaveretum + atropine	,, ,,	,,	Pinkerton cuirass. Lignocaine + adrenaline to cords, etc.	,, ,, ,,	Oxygen into suction tube of bronchoscope. Thiopentone + suxamethonium as required	
Present series	Atropine	Thiopentone 12·5 mg. stone; gallamine 0·75 mg./stone	50 mg. suxamethonium	Hyperventilation with 10 l. nitrous oxide and 5 l. oxygen, using a non-rebreathing technique	Complete apnoea. Manual compression of chest	Nitrous oxide and oxygen mixture (10: 5)	

* TCE = Trichlorethylene.

We thank the surgeons and anaesthetists of the London Chest Hospital for their co-operation, and in particular Mr. J. R. Belcher, who allowed us to use the method in his out-patient clinic.

REFERENCES

Bayuk, A. J. (1957). *Anesthesiology*, **18**, 135.
Buck, H. A. (1955). *Anaesthesia*, **10**, 313.
Cheatle, C. A., and Chambers, K. B. (1955). Ibid., **10**, 171.
Churchill-Davidson, H. C. (1952). Ibid., **7**, 237.
—— (1953). Ibid., **8**, 128.
Doughty, A. (1957). *Brit. J. Anaesth.*, **29**, 407.
Green, R. A., and Coleman, D. J. (1955). *Anaesthesia*, **10**, 369.
Herron, R. A. C. (1950). Ibid., **5**, 40.
Kelsall, P. D. (1954). *Brit. J. Anaesth.*, **26**, 182.
Kovacs, S. (1957). *Anesthesiology*, **18**, 335.
Macintosh, R. R. (1954). *Anaesthesia*, **9**, 77.
Mathewson, H. S., McIntyre, J. D., and Meriwether, D. R. (1956). *Anesthesiology*, **17**, 623.
Morris, D. D. B., and Dunn, C. H. (1957). *Brit. med. J.*, **1**, 383.
Pinkerton, H. H. (1957). *Brit. J. Anaesth.*, **29**, 421.
Toker, P. (1955). *S. Afr. med. J.*, **29**, 40.

HAZARDS WITH LOCAL ANAESTHETICS DURING BRONCHOGRAPHY AND BRONCHOSCOPY

BY

SAMIR KUMAR GUPTA, M.B., M.R.C.P.Ed.
Medical Registrar, Islington Chest Clinic and Whittington Hospital, London

Since 1935 amethocaine hydrochloride, which belongs to the procaine group, has been widely used as a local anaesthetic by chest physicians and surgeons. A notable advance in 1943 was the introduction of lignocaine, a drug chemically allied to acetanilide. Lignocaine is regarded as a very safe drug (Hewer and Lee, 1957). Surprisingly, in Britain there have been few published case reports regarding the hazards of these drugs during bronchoscopy and bronchography, though reactions to amethocaine have been described (Hancock, 1939; Jackson, 1949). Here are reported five examples of untoward reactions to these drugs.

Our techniques for bronchoscopy and bronchography are as follows. For premedication we use butobarbitone, 3 gr. (0.2 g.), 90 minutes before bronchography. A subcutaneous injection of atropine sulphate, 1/100 gr. (0.65 mg.), is given one hour later, and simultaneously the patient begins to suck slowly a tablet of amethocaine (65 mg.). On arrival at the *x*-ray department the patient often spits out the remainder of the tablet when about 2–4 ml. of 4% lignocaine solution is slowly delivered over the back of the tongue into the tracheobronchial tree. Bronchography is usually carried out by "spoon-technique." For bronchoscopy the premedication is either morphine (or pethidine) with atropine sulphate in the usual dosage. Half an hour before the procedure the patient starts sucking amethocaine. In the operation theatre the throat is painted with 2 ml. of 4% lignocaine solution and the tracheobronchial tree is anaesthetized with 0.5% solution as spray.

Case Reports

Case 1.—In 1954 a boy aged 16 was admitted to hospital with a chronic productive cough. Prior to bronchography he was given 65 mg. of amethocaine to suck at 1.45 p.m. At 2.15 p.m. 8 ml. of amethocaine (2%) was administered through a nasal catheter, but was immediately coughed out. A further 8 ml. was given. Within two minutes he became giddy and semicomatose. The catheter was taken out immediately. He rapidly became unconscious, with widely dilated pupils, not reacting to light. Cyanosis and vomiting soon followed, but there was no convulsion. His pulse and blood pressure remained normal throughout. Oxygen was delivered through a mask and his pharynx was repeatedly aspirated. Half an hour later he regained consciousness, with residual confusion. An uneventful bronchoscopy was carried out later under nitrous oxide and oxygen anaesthesia.

Case 2.—A housewife aged 27 had had pulmonary tuberculosis since 1952. On September 8, 1955, a left upper lobectomy with a left apical thoracoplasty was performed. On September 10 *x*-ray examination showed a collapsed left lower lobe. Bronchoscopy was immediately arranged. At 3.15 p.m. the back of her throat and pyriform fossa were painted with 2 ml. of 2% amethocaine solution. She at once developed a severe headache. Unconsciousness with a convulsion rapidly followed. She became very pale and cyanosed, her pulse became thready, and her blood pressure was unrecordable. Immediate artificial respiration was begun with oxygen through a mask. Intravenous thiopentone sodium (500 mg.) was given while blocks were placed under the foot of the bed. The trachea and pharynx were frequently aspirated. Improvement quickly followed the administration of intravenous thiopentone. At 4 p.m. nikethamide (250 mg.) was administered intravenously. By 5 p.m. she was merely semicomatose. One hour later she was conscious, although very weak, was slightly confused, and had hypotension (90 mm. Hg). Next morning she was normal.

Case 3.—A 50-year-old housewife came for a bronchogram in August, 1955. One amethocaine lozenge (65 mg.) was given to suck, followed by local instillation of 2% amethocaine (4 ml.) down her air passage. She immediately complained of intense headache and giddiness. She became semicomatose, and remained so for 15 minutes. The foot of the bed was raised on blocks and a careful watch was kept on her. One hour later she was again normal. The bronchography was carried out uneventfully.

Case 4.—A housewife aged 25 was admitted to hospital with increasing dyspnoea on exertion. She had signs of a tight mitral stenosis with sinus rhythm, and also signs of left basal bronchiectasis. Three weeks later, at 2 p.m., she was given one amethocaine lozenge (65 mg.) to suck. The trachea was anaesthetized with 4 ml. of 4% lignocaine solution and within 15 minutes she appeared to be comatose. At 3.30 p.m. she was deeply unconscious, apnoeic, and cyanosed. Artificial respiration and oxygen administration were begun. Intravenous nikethamide (250 mg.) was given, and was repeated twice. She had no convulsion. Solution of adrenaline hydrochloride, *B.P.* (0.5 ml.), was given subcutaneously. Repeated rigors followed. After two hours of artificial respiration breathing was resumed, but she did not regain consciousness until 7 p.m. She remained confused till late at night. Next morning she was quite normal.

Case 5.—A woman aged 32 was arranged to have a bronchial lavage. Sucking of an amethocaine lozenge (25 mg.) was uneventful. Fifteen minutes later, 1 ml. of 4% lignocaine was poured over the back of the tongue. She complained of immediate palpitation, with tingling and numbness over her right hand. She became pale, sweated, and was slightly breathless. She appeared normal in about 10 minutes, but complained of numbness for another hour. Lavage was done uneventfully.

Discussion

In this series, Case 5 was undoubtedly hypersensitive. Case 2 was probably also hypersensitive, as the symptoms appeared immediately following the amethocaine paint. In Case 4 it is difficult to determine the offending drug; lignocaine might have been responsible, as the drowsiness appeared shortly after its administration, and the pattern of symptoms supports this view (Morrisset, 1957). Case 1 was a definite case of toxicity: this patient had at least four times the safe

dosage of amethocaine; moreover, it was administered through a nasal catheter—a very dangerous method, as pointed out by Steinhaus (1952). Case 3 was probably a case of toxicity to the same drug. No history regarding previous sensitization to local analgesics was available in any of the cases. None of these patients had suffered from any obvious allergic disorder, except Case 4.

Summary

Five cases of hypersensitivity and/or toxicity to amethocaine and lignocaine during bronchoscopy and bronchography are reported.

I thank Drs. J. V. Davies, H. D. Palmer, and N. Whittaker for allowing me to publish these cases. I am indebted to Dr. R. H. Elphinstone for supplying the details for Case 3.

REFERENCES

Hancock, P. E. T. (1939). *Proc. roy. Soc. Med.*, **32**, 538.
Hewer, C. L., and Lee, J. A. (1957). *Recent Advances in Anaesthesia and Analgesia*, 8th ed., p. 121. London.
Jackson, C. A. (1949). *Brit. med. J.*, **1**, 99.
Morrisset, L. M. (1957). *U.S. armed Forces med. J.*, **8**, 741.
Steinhaus, J. E. (1952). *Anesthesiology*, **13**, 577.

Medical Memoranda

Subacute Delirious State due to "Preludin" Addiction

"Preludin" (2-phenyl-3-methyl-tetrahydro-1,4-oxazine hydrochloride) has been introduced as a safe treatment for obesity by controlling appetite. The case described below is of interest as an illustration of preludin addiction causing a subacute delirious state, with auditory hallucinations and visual illusions, merging into the dysmnesic syndrome.

CASE REPORT

The patient was a single young woman aged 23. At the age of 17 she began taking dexamphetamine sulphate tablets, and two years later had reached her maximum dosage of 17 5-mg. tablets daily. She had been admitted to a mental hospital twice suffering from irritability, restlessness, and difficulty in carrying on as a student nurse. When the drug became no longer freely available on request she began purchasing preludin instead, increasing the dosage until, after 18 months, she was taking 20 tablets daily.

On August 23, 1957, I visited the patient at her home. She was a young woman of average build who was reluctant to enter into rapport to any real extent. She was restless and elated and had a shallow insipid smile on her face throughout the interview. At intervals she broke into outbursts of laughter that had no obvious relevance to her conversation. There was some clouding of consciousness, and it was difficult to hold her attention for an appreciable length of time. During the examination her condition fluctuated, and at times her thinking became incoherent and frankly confused.

After admission to the psychiatric department of a general hospital she remained elated and had periods of moderate confusion. On the day of admission (August 31), and during one of her lucid periods, she stated that she had heard voices speaking to her three months previously and indicated that she had apparently experienced visual illusions. She added, "I imagined I heard voices. They said, 'Pray hard.' I saw one or two hallucinations—things moving. The mirror would move, then the wall, and then the window." There was memory impairment, particularly for recent events. She gave the date as August 2, 1957, and thought the Prime Minister was President Truman. She was very slow and hesitant in concluding that she had only come into hospital on the day she was being examined.

The personal history showed that when 17¼ years old she began training as a nurse but would rarely arrive on duty in time. She failed one of her examinations, had a row with the matron, and was finally discharged from the course. She ran away from her mother and lived in a convent for a short period. For three years prior to admission to hospital she associated with a married man, sexual intercourse having occurred. The history contained nothing else of note. Her mother was a highly strung, irritable woman. Her eldest brother was a nervous individual who suffered from "twitches." A sister had attempted suicide.

After admission she was placed on paraldehyde, 2–3 dr. (7–10.5 ml.) p.r.n., and "parentrovite" (vitamin-B complex and ascorbic acid), 7 ml. of the "high potency" preparation intramuscularly, daily for one week, followed by the "maintenance" preparation, 4 ml. intramuscularly daily for a further week. Subsequently she was placed on "orovite" (vitamin-B complex), 2 tablets t.d.s., and tabs. vit. C., 100 mg. t.d.s.

She responded to treatment quickly. She became more composed and her confusion and elation subsided. Following the rapid improvement in her frank psychotic state, she insisted on leaving hospital, against advice, on September 17.

COMMENT

This is a further example of addiction to preludin with a resultant toxic psychosis. Like Bethell's (1957) patient her history showed evidence of marked instability. In addition the family history was adverse. The tendency to preludin addiction therefore would appear to be in line with that recognized for amphetamine sulphate in particular, if not for addiction in general—namely, its restriction to neurotic and psychopathic personalities.

For six months before admission she had been on her maximum dosage of preludin. This phase coincided with the period when she was off work, and it was during this time that she was having sexual relations with her boy friend. It seems possible, therefore, that the drug may have played some part in producing sexual excitement, this being a feature that has been recognized in amphetamine addiction (Bleuler, 1949).

Bethell's patient required approximately 12 preludin tablets in order to experience a similar effect to that produced by "a few" tablets of dexamphetamine. However, Randell (1957) gained the impression that preludin was more powerful than amphetamine. The case reported lends support to the findings of Bethell in so far as after two years' habitual usage the maximum number of dexamphetamine tablets taken was 17, whereas after 18 months' addiction to preludin the maximum number of tablets required was 20. This finding also gives limited support to the claim of the manufacturers that the drug's effect on the nervous system is weaker than that of amphetamine. Thomä and Wick (1954) also concluded, on the basis of experiments with unanaesthetized dogs, that the quantity of preludin needed was six times that of amphetamine to produce the equivalent degree of excitement.

This patient showed fluctuating clouding of consciousness, incoherence of thought, and moderate confusion—the essential features of the "subacute delirious state" (Mayer-Gross, Slater, and Roth, 1954). Also, she had experienced auditory hallucinations and visual illusions, and subsequently she developed the

characteristic symptoms of the dysmnesic syndrome. A clinical picture such as this provides further justification for the view that preludin should not be made freely available to the public, but should be restricted in its sale by placing it on the First and Fourth Schedules of the Poisons Rules.

MAURICE SILVERMAN, M.D., D.P.M.,
Consultant in Psychological Medicine,
Blackburn Group of Hospitals.

REFERENCES

Bethell, M. F. (1957). *Brit. med. J.*, **1**, 30.
Bleuler, M. (1949). In E. Bleuler's *Lehrbuch der Psychiatrie*, 8th ed., edited by M. Bleuler, p. 326. Springer, Berlin.
Mayer-Gross, W., Slater, E. and Roth, M. (1954). *Clinical Psychiatry*, p. 296. Cassell, London.
Randell, J. B. (1957). *Brit. med. J.*, **2**, 508.
Thomä, O., and Wick, H. (1954). *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **222**, 540.

Pancreatico-gastric Fistula due to Giant Gastric Ulcer

Posterior penetration is a relatively common complication of gastric ulceration, being noted in 15–20% of patients treated surgically (Haubrich, Roth, and Bockus, 1953). In most cases the pancreas is the organ which is penetrated (Ruffin, 1951), but no reports have been found describing the transection of the main pancreatic duct by the ulcerative process. In the following case a giant gastric ulcer had destroyed a segment of the duct 2 cm. long, with the result that the pancreatic secretion was being discharged into the stomach.

CASE REPORT

A 72-year-old man was admitted to hospital complaining of increasingly severe epigastric pain for four years. He had lost some weight, and had had a small melaena. On examination there was marked tenderness in the left hypochondrium. A barium-meal examination revealed a very large gastric ulcer on the lesser curve, but there was no reflux of barium along the pancreatic duct.

At operation a benign ulcer, 3.5 cm. in diameter, was found midway along the lesser curvature of the stomach, penetrating posteriorly into the pancreas. The ulcer was "nipped" off the pancreas without undue difficulty, and a two-thirds gastric resection and Billroth I anastomosis were performed. At the end of the operation, when the pancreas was again drawn forward in order to dust the ulcer floor with penicillin powder, it was found that a segment of the main pancreatic duct 2 cm. long had been completely destroyed by the ulcer. The divided ends of the duct were clearly visible at each side of the ulcer crater, and from them pancreatic juice was flowing rapidly. It was possible to pass a small rubber tube (3 mm. diameter) into the left part of the duct, but not into the right part.

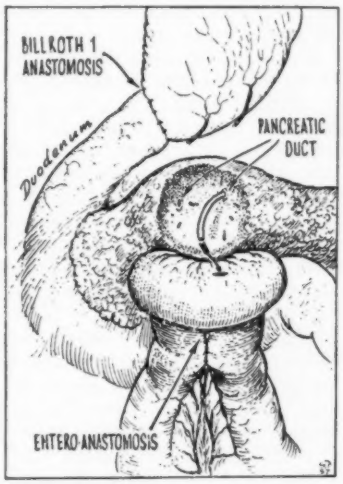
Most of the pancreatic secretion was pouring into the peritoneal cavity, and it was therefore decided to anastomose the ends of the divided duct to a defunctioned loop of bowel. An entero-anastomosis was made across the base of a proximal loop of jejunum, which was then brought up behind the transverse colon. The friable ends of the divided duct were unsuitable for direct anastomosis to the jejunum. An opening 1 cm. long was therefore made in the apex of the loop, and through this opening was threaded the end of the rubber tube previously passed into the left portion of the pancreatic duct (see Fig.). The top of the loop was then carefully stitched to the edges of the ulcer crater on the pancreas, and the remains of the gastro-colic omentum were tacked around it.

As soon as he recovered consciousness the patient was given 30 mg. of propantheline bromide ("pro-banthine"), and subsequently received 15 mg. three times a day, with an additional 30-mg. dose each night for 10 days. Recovery was uneventful, and 16 days after operation the piece of fine rubber tubing was passed.

Nine months later the patient was free from symptoms and gaining weight. There was no evidence of pancreatic insufficiency or cyst formation.

COMMENT

The accessory pancreatic duct is sometimes injured by a penetrating duodenal ulcer, or during the performance of subtotal gastrectomy for this type of ulcer (Millbourn, 1949). The relative immunity to injury of the main pancreatic duct is surprising, since the duct is situated in the antero-superior part of the body of the pancreas close to the common site of gastric ulceration (Millbourn, 1949). The wall of the main duct may be more resistant to erosion and destruction by the ulcerative process than is the remainder of the gland tissue. Alternatively, some of the cases of external pancreatic fistulae which develop after gastrectomy may be due to failure to notice at operation that part of the main duct had been damaged or destroyed. Careful inspection of the crater may be necessary to detect the ends of the ducts; a final inspection just before closing the abdomen may reveal a considerable quantity of pancreatic juice in the vicinity of the pancreas.



A drawing of the operative procedure employed.

If a divided duct is found it must be decided, by probing or injecting dye, whether it is the main or the accessory duct. The ends of the accessory duct can be ligated with unabsorbable thread (R. B. Cattell, 1957, personal communication), but if part of the main duct has been destroyed some type of pancreatico-intestinal anastomosis will be necessary; the details of the actual procedure employed will depend on the site and size of the fistula. Propantheline bromide is a powerful inhibitor of pancreatic secretion (Sinclair, 1956), and its administration in the immediate post-operative period may help to protect the anastomosis until the risk of leakage has passed.

We are grateful to Mr. G. A. Smith for the drawing.

M. LAVERY, M.Sc., F.R.C.S., F.R.C.S.Ed.,
Senior Surgeon, Belfast City Hospital.
J. KYLE, M.Ch., F.R.C.S., F.R.C.S.I.,
Lecturer in Surgery, University of Liverpool.

REFERENCES

Haubrich, W. S., Roth, J. L. A., and Bockus, H. L. (1953). *Gastroenterology*, **25**, 173.
Millbourn, E. (1949). *Acta chir. scand.*, **98**, 1.
Ruffin, J. M. (1951). In *Peptic Ulcer*, edited by D. J. Sandweiss, p. 685. Saunders, Philadelphia and London.
Sinclair, I. S. R. (1956). *Brit. J. Surg.*, **44**, 250.

Reviews

SOCIAL SURVEYS

Survey Methods in Social Investigation. By C. A. Moser. (Pp. 352+xiv. 35s.) London: William Heinemann, Ltd. 1958.

This is the third book on social surveys to be produced in Britain in recent years. Abrams and Caradog Jones wrote mainly for the general reader. Mr. Moser has produced a textbook for the student, and an excellent job he has made of it.

The author takes us systematically through the subject. There are chapters on documents and techniques of observation; mail questionaries, interviewing, and recording schedules; and a very full discussion in about 100 pages of sampling, with many references to the unfamiliar world of market research and advertising as well as to the Government's social survey. The account of types of sample design—random; stratified; multi-stage; quota; panel methods which have quite special possibilities for use in the health field; etc.—is outstanding and good enough reason in itself for getting this book. There are in addition discussions of "response" and other "error," and a brief account of coding, tabulation, and presentation. Mr. Moser writes clearly, with plenty of illustration from a wealth of experience. He is master of his subject and a good teacher (though if Muncie, Indiana, is a "large city" (p. 170), what is Birmingham ?).

Medical readers will be disappointed with the chapter on interviewing: surely there is much more to interviewing than is said or implied in this presentation. In general, workers in social medicine will be saddened by the small impression their labours seem to have made on those engaged in neighbouring fields. Thus Mr. Moser's discussions of prospective versus retrospective studies, of observer variability, and of the biases introduced by the refusal of some of the selected to take part in a survey would all have benefited from a closer acquaintance with medical work in progress. As a social scientist (not Mr. Moser) might put it, interdisciplinary methodologic communication among the behavioral sciences is at a stage of underdevelopment. In 1953 and again in 1957 medical research workers in Britain addressed earnest appeals to social scientists for help, with small success. Perhaps a change of tactics is indicated; perhaps we might emphasize more what we could contribute to the social sciences.

This book is a "must" for academic departments of social medicine. The medical officer of health beset with the difficulties of investigating the use made of his child welfare services, the smoking habits of his schoolboys, employment among married women, leisure interests of industrial workers, the exercise taken by middle-aged men, or the contacts, activities, and domestic circumstances of his 65-year-olds will find Mr. Moser's book full of relevant material, easy to read, always helpful, and thoroughly dependable.

J. N. MORRIS.

MEDICINE IN SOUTH AFRICA

A History of Medicine in South Africa up to the End of the Nineteenth Century. By Edmund H. Burrows. (Pp. 389; illustrated. 63s.) Capetown: A. A. Balkema. London: Paul Koston. 1958.

This book is a valuable mine of general and medical information about South Africa. It contains over 200 short biographies of doctors and is documented by 1,869 references. It must at once become a standard reference book for South African medicine.

In the late seventeenth century, when ships took the long route to India, a large proportion of every crew fell sick on the way, from scurvy and other diseases, and Capetown arose from the need for a place for refreshment, and for putting on shore those who were very ill and in urgent need of special care. It was indeed a "scurvy" station. At first Dutch surgeons were in charge, but in the early nineteenth century British military surgeons played a larger part. Dutch and British settlers increased the population and gradually extended up country. Then came the diamond and the gold rushes which changed the face of South Africa.

What a variety of doctors come into the picture: Dr. W. G. Atherstone, who was also a geologist and identified the first diamond which had been picked up along the Orange River; Dr. Starr Jameson, who led the famous raid; Dr. Barry, who did good work in South Africa and later rose to be Inspector-General of Army Hospitals, and when he died was found to be a woman; and Dr. (later Sir) Andrew Smith, who, though more widely known because of Florence Nightingale's criticisms, was a deservedly distinguished officer in South Africa; not to mention the famous Dr. Sauer, who was stabbed by a fork in a non-vital part by the chef whom he had irritated beyond endurance.

One point of criticism. Though many of the biographies are most interesting, they are inserted in the text and interrupt the smooth flow of the story. It might be worth considering whether they should be put all together at the end of the main story.

ZACHARY COPE.

RADIOTHERAPY IN VIENNA

Röntgentherapie. By Georg Fuchs, M.D. (Pp. 238+viii; illustrated. DM. 28.) Munich and Berlin: Urban und Schwarzenberg. 1958.

Radiotherapists in Britain have been fortunate in that they have had at their disposal for some years now radiations of high energy, whether from supervoltage *x*-ray or cobalt teletherapy apparatus. The improvement in the comfort of patients during and after treatment and the results of treatment of cancer in certain regions—for example, larynx and bladder—have been so great that treatment of these conditions by conventional deep *x*-ray therapy is now considered obsolete. Accordingly, a work on radiotherapy which, like the present volume, is designed mainly for radiotherapists who have at their disposal only *x* rays of an energy no higher than 250 kV will find little appeal here. The fact must, however, be faced that, apart from the United States, Canada, and Britain, this is the best equipment generally available in most countries, and therefore this book will meet a definite need.

Within its own limits this introduction to *x*-ray therapy is a useful work. The introductory physics is adequate and well presented; the radiobiological section perhaps less so. The excellent chapter on the general principles of cancer therapy by *x* rays is followed by a systematic summary of the treatment recommended in disease of the various regions of the body. Not all radiotherapists would agree with the methods advocated in non-malignant disease; certainly many would disagree with the statement that irradiation of the tonsils and cervical lymph nodes for chronic tonsillitis in childhood is completely free from danger and is strongly to be

recommended. The book is well produced and illustrated and gives an interesting view of present-day radiotherapy in Vienna.

WALTER M. LEVITT.

NEUROLOGICAL BASIS OF BEHAVIOUR

Ciba Foundation Symposium on the Neurological Basis of Behaviour. In Commemoration of Sir Charles Sherrington, O.M., G.B.E., F.R.S., 1857–1952. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. (Pp. 400+xii; illustrated. 52s. 6d.) London: J. and A. Churchill, Ltd. 1958.

In 1957, the centenary of the birth of Sir Charles Sherrington, the Ciba Foundation arranged this symposium, which was attended by 34 distinguished scientists and at which the 19 papers published in this volume were delivered. The majority deal with experimental work on animals, but Penfield discusses the role of the temporal cortex in recall of past experience and interpretation of the present on the basis of cortical stimulation studies in man, and there is a fascinating chapter by Magoun on the early history of ideas relating the mind and the brain. Much of the book is difficult reading for one not engaged in neurophysiological research, but the effort is worth while, for there is collected here the experimental results and stimulating ideas of many of the leading workers on a subject of increasing contemporary importance—the organic basis of behaviour. After each paper there is in small type a verbatim report of the discussion, and in some cases this is as interesting as the papers themselves.

J. W. ALDREN TURNER.

SUPERFICIAL

Personality, Appearance and Speech. By T. H. Pear, M.A., B.Sc. (Pp. 167. 15s.) London: George Allen and Unwin Ltd. 1957.

It is perhaps unfair to complain of Professor Pear's latest book that it is superficial; for it is the superficial appearances of mankind—the dress, the face, the hair, the voice, the laugh, the accent, the speech—with which his book is concerned. Personality, he defines as "the effect upon others of a living being's appearance, behaviour, etc., so far as they are interpreted as distinctive signs of that being"—a Berkeleian definition neither elegant nor convincing, since if there is no observer personality disappears, unlike Monsignor Knox's tree, which

"Continues to be
Though no one's about in the quad."

The method of the book is descriptive and observational, as will be seen from these quotations: "A doctor whose special subject concerned facial appearance said, 'I must always wear a bowler because of my lowborn face.'" And, "Possessions can be signs of personality. A medical specialist buys a large car, because a small one might embarrass the G.P. who has asked him to visit a private patient." And again, "The new National Health Service had sent to spectacle-makers thousands of women who bought rims of different colours to fit the same pair of spectacles and to match their dresses. Soon jewels were set into the rims, and the shape of the lenses altered to 'suit' or call attention to the face." Such observations provide no yardstick for the measurement of personality.

How is it that sociological and anthropological data which are interesting enough when they describe inhabitants of Bali or Tahiti make tedious reading when they depict ourselves?

D. V. HUBBLE.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Cultivos Celulares en el Diagnostico de las Enfermedades Virales. By Dr. Luis Baquerizo Amador. (Pp. 84; illustrated.) Guayaquil: University of Guayaquil. 1958.

Doctor Squibb. The Life and Times of a Rugged Idealist. By Lawrence G. Blochman. (Pp. 371+xii; illustrated. $5.) New York: Simon and Schuster. 1958.

Healthful Living. Some Fundamentals of Public Health. (Pp. 88.) Adelaide: South Australia Department of Public Health. 1958.

Medical Department, United States Army. Surgery in World War II. Neurosurgery, Volume I. Prepared and published under the direction of Major-General S. B. Hays; Editor in Chief: Colonel J. B. Coates, jun., M.C. Editors for Neurosurgery: R. G. Spurling, M.D., B. Woodhall, M.D. Associate Editor: Elizabeth M. McFetridge, M.A. (Pp. 466+xix; illustrated. $5.) Washington, D.C.: Office of the Surgeon-General, Department of the Army. 1958.

Opera et Opuscula Collecta. Edidit Institutum Clinices Universitatis Upsaliensis. Vol. X-XI. Edited by Erik Ask-Upmark. Uppsala: Almqvist and Wiksells. 1958.

Ciba Foundation Symposium on Medical Biology and Etruscan Origins. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. (Pp. 255+xii; illustrated. 45s.) London: J. and A. Churchill Ltd. 1959.

Biochemistry in Relation to Medicine. By C. W. Carter, M.A., B.M., B.Ch., R. V. Coxon, M.D., D.Phil., D. S. Parsons, M.A., D.M., and R. H. S. Thompson, M.A., B.Sc., D.M. Third edition. (Pp. 628+xiii; illustrated. 50s.) London, New York, Toronto: Longmans, Green and Co. 1959.

Ego Psychology and the Problem of Adaptation. By Heinz Hartmann. Translated by David Rapaport. (Pp. 121+xi. 21s.) London: Imago Publishing Co. Ltd. 1958.

The Central Nervous System and Behavior. Transactions of the First Conference, February 23, 24, 25, and 26, 1958. Edited by Mary A. B. Brazier, Ph.D. (Pp. 450; illustrated. $5.25.) New York: Josiah Macy, Jr., Foundation. 1959.

Ecological Processes. By Alan Mozley, D.Sc., Ph.D., F.R.S.E. (Pp. 68+xi. 9s.) London: H. K. Lewis and Co. Ltd. 1959.

Physiology of Fungi. By Vincent W. Cochrane. (Pp. 524+xiii; illustrated. 78s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall, Ltd. 1958.

Melanoblasts and Melanocytes in Fetal Negro Skin. By Arnold Zimmermann and Samuel W. Becker, jun., M.D. (Pp. 59; illustrated. $2.25.) Urbana, Illinois: University of Illinois Press. 1959.

The Organic Psychoses. A Guide to Diagnosis. By John G. Dewan, M.A., M.D., Ph.D.(Cantab.), D.P.M.(Eng.), F.R.C.P.(C.), F.A.C.P., F.A.P.A., and William B. Spaulding, M.D., F.R.C.P.(C.). (Pp. 170+xiii; illustrated. 48s.) Toronto: University of Toronto Press. London: Oxford University Press. 1958.

Clinical Epidemiology. By John R. Paul, M.D., Sc.D. (Pp. 291+xii; illustrated. 37s. 6d.) Chicago: University of Chicago Press. London: Cambridge University Press. 1958.

Gusa Endemica. Distrofia Endemica. Tireopata. Cercetari Monografice, Clinice si Experimentale. Edited by St.-M. Mîlcu. Vol. 2. (Pp. 454; illustrated.) Bucharest: Editura Academiei Republicii Populare Romine. 1958.

Biblioteca Medicala X. Gripa. Aspecte din Problema. By Adelina Derevici. (Pp. 472.) Bucharest: Editura Academiei Republicii Populare Romine. 1958.

Hernias Diafragmáticas. (*En el Adulto y en el Niño.*) By Dr. Alfredo J. F. Cesanelli and Dr. Juan José Boretti. (Pp. 344; illustrated.) Apartado de las Actas de la Asociación Argentina de Cirugía. 1958.

Contribución al Estudio de las Demencias Preseniles. (*Enfermedades de Alzheimer y Pick.*) By Ricardo Pons Bartran. (Pp. 135; illustrated.) San Baudilio de Llobegrat: Informaciones Psiquiátricas, Vol. 3, No. 1. 1958.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MARCH 14 1959

LIVE POLIOMYELITIS VACCINE

Dr. Albert B. Sabin is the leading advocate of living attenuated vaccines against poliomyelitis. Few, if any, other authorities can claim such great experience in this field. The living vaccines now being tested in many parts of the world are mostly those that he has developed and prepared. His long article in the opening pages of this issue presents his views on four important aspects of the subject with a wealth of welcome technical detail. It deserves the closest attention.

A safe and effective living attenuated poliomyelitis vaccine would be easier to make and administer than is the present formolized vaccine, would probably come nearer to eliminating paralytic poliomyelitis, and, unlike formolized vaccine, might be used to stop an actual or threatened epidemic. These are strong reasons for continuing the search for such a vaccine.

The formolized vaccine is thought to act by raising the level of circulating antibodies which block the passage of virus from the alimentary canal to the central nervous system. It does not, as Sabin clearly shows, prevent the virus from infecting the alimentary canal. To be fully effective, it must be given in three or more widely spaced doses, a fact which limits its use as an emergency measure in epidemic control. Moreover, we do not, and cannot for some years, know how effective formolized vaccine is. As Dr. J. Knowelden[1] pointed out in a paper published in last week's *Journal*, current beliefs about the efficacy of formolized vaccine rest on two field trials made in 1954 and 1956 (the latter too small to give much quantitative precision) and on measurements of neutralizing antibody produced by vaccination. Such measurements are not completely reassuring. Elsewhere in this issue (p. 680) Dr. F. T. Perkins, Miss Risha Yetts, and Professor W. Gaisford report a disappointing antibody response in very young children, and the recent report[2] from the Biological Standards Control Laboratory in London shows that many older subjects respond poorly to the important type 1 component after the usual three injections. Nothing can yet be inferred about the efficacy of formolized vaccine from the incidence of paralytic poliomyelitis in countries where vaccination has been widely practised. While it seems likely that a full course of the formolized vaccine gives a substantial measure of protection against paralytic poliomyelitis, the overall prophylactic effect of the vaccine may prove to be less than the early trials suggested; and it is unlikely to reduce the amount of virulent virus at large in the population.

Sabin presents evidence, which others support, that living attenuated virus can prevent infection of the intestine with other strains of poliomyelitis virus. There is reason to think that it can do this very soon after its ingestion, so that widespread use of a living vaccine might interfere with epidemic spread of virulent strains and ultimately displace such strains from the community. It is also clear that living attenuated virus can pass by natural means from children who have ingested it to their family contacts and others—a very useful characteristic if the vaccine can be guaranteed to remain safe in spite of passage through a series of human intestines.

Up to this point there is general agreement among virologists; and it is also agreed that, to be usable, a living attenuated virus must be incapable of reversion to dangerous neurotropism as a result of its uncontrolled multiplication in a human population. Unfortunately, nearly all who have studied the matter have found that virus isolated from the faeces of those who have been infected with living attenuated vaccine commonly possesses rather more neurotropism than that of the vaccine itself. Such has been the experience of Sabin, and of other workers quoted by him, including A. A. Smorodintseff, in Russia, G. W. A. Dick and D. S. Dane, in Northern Ireland, and S. K. R. Clarke and his co-workers in England. In his paper Sabin describes in detail his methods for measuring neurotropism, and criticizes the methods and conclusions of others who have done this; but he does not dissent from the conclusion that some small restoration of neurotropism commonly occurs during passage of the virus through the human intestine. All agree that the observed increase in neurotropism is small, even, as Smorodintseff has shown, after serial passage through a number of children.

It is possible that Sabin's highly attenuated vaccine strains, which are able to attack lower-motor neurones only when injected into their immediate vicinity in the spinal cord, have permanently lost the power to invade and spread in the central nervous system by natural pathways. The difficulty is to prove that this is so. Laboratory evidence, and the

[1] Knowelden, J., *Brit. med. J.*, 1959, 1, 620.
[2] "Antibody Response of Adolescents and Adults to a Booster Dose of Poliomyelitis Vaccine." ibid., 1959, 1, 609.
[3] *Wld Hlth Org. tech. Rep. Ser.*, No. 145, 1958. Geneva.

evidence based on study of vaccine strains which have been restored to the human intestinal environment for a comparatively short time, have so far been reassuring on this point, but one has to remember that the genetic behaviour of poliomyelitis virus is not yet perfectly understood, and also that there is much in the natural history of poliomyelitis, as for instance its seasonal behaviour, which is not yet explained. We do not know whether naturally occurring strains alter their neurotropism significantly "in the field"; but, if they do, it is difficult to see why laboratory-selected strains should not do so too, though we know nothing of the circumstances in which this might happen, nor even whether it can happen.

The one topic on which the opinions of virologists have been divided is the choice of method to use to settle this difficult question. One school, led by Dr. Sabin and a W.H.O. Expert Committee,[3] considers that large-scale studies like those which Sabin mentions as already in progress in Singapore, Czechoslovakia, and the U.S.S.R. are justifiable and now urgently needed. The more conservative school, fearing the widespread dissemination of virus of uncertain mutability, particularly in countries where "wild" virus is relatively uncommon, would rather allow the evidence of smaller, more rigidly controlled studies to accumulate first, hoping that a better understanding of the mutation of poliomyelitis virus will develop *pari passu*. Agreement on this question can come only as the result of new information and continued full interchange of data and views.

Judging from Sabin's description of it, the trial which J. H. Hale has been conducting in Singapore, the result of which should soon be known, may be highly important. In it, according to Sabin, type 2 vaccine has been given to 200,000 children during the course of a type 1 epidemic. If vaccine of one type used during an epidemic due to another type is shown to have modified the epidemic, a fresh approach to certain questions will be needed. Sabin points out that living attenuated vaccine can prevent subsequent infection of the intestine with another strain of virus whether demonstrable circulating antibody is produced or not. He postulates some kind of cellular immunity on the part of the intestinal wall, independent of the immunity produced by formolized vaccine which depends on circulating antibody. If such a cellular immunity exists, to what extent is it, like the serological immunity, type specific? How long does the non-receptive state in the intestine persist after vaccination?

Many other questions remain to be answered. Further human trials, on whatever the scale, are needed. It remains to be seen whether the results of those already performed and now in progress give sufficient guarantee of safety to secure agreement that further widespread use of living vaccines is justified: the safety yet to be guaranteed is the safety of those who acquire the vaccine strains by natural means perhaps months or years after widespread vaccination has been practised in a country. Whichever side one takes in this controversy, it is impossible not to admire and be grateful for the skill, labour, and courage which have carried the research to its present exciting phase.

THE PENICILLIN NUCLEUS

A recent report[1] from the Beecham Research Laboratories of the isolation of 6-aminopenicillanic acid from penicillin fermentations has received a surprising amount of publicity. 6-Aminopenicillanic acid is the nucleus of the penicillin molecule without a side-chain, in other words a desacyl penicillin. When treated with phenylacetyl chloride it yields a phenylacetyl derivative identical with penicillin G, and when treated with phenoxyacetyl chloride it yields penicillin V. A series of penicillins with different side-chains may clearly be obtained from it by analogous reactions.

The formation of 6-aminopenicillanic acid during the production of penicillin has been suspected for some time. In 1953 K. Kato[2] concluded from good indirect evidence that it was present in fermentations with *Penicillium chrysogenum* to which no side-chain precursor had been added. The results obtained by H. R. V. Arnstein and others in their studies on the mechanism of the biosynthesis of penicillin were consistent with the view that acylation of the nucleus was a final step in the production of the active molecule.[3] Nearly ten years ago Japanese workers claimed to have removed the side-chain from penicillin G by an enzyme preparation from *Penicillium chrysogenum* and to have obtained 6-aminopenicillanic acid in crystalline form.[4] But many attempts to repeat these experiments have been unsuccessful. The report by F. R. Batchelor and colleagues[1] in *Nature* must thus rank as the first acceptable publication of the isolation of 6-aminopenicillanic acid from a natural source. Their work

[1] Batchelor, F. R., Doyle, F. P., Naylor, J. H. C., and Rolinson, G. N., *Nature (Lond.)*, 1959, **183**, 257.
[2] Kato, K., *J. Antibiot.*, 1953, **6**, 130, 184.
[3] Arnstein, H. R. V., and Crawhall, J. C., *Biochem. J.*, 1957, **67**, 180.
[4] Sakaguchi, K., and Murao, S. I., *J. agric. chem. Soc. Japan*, 1950, **23**, 411.
[5] Sheehan, J. C., in *Amino Acids and Peptides with Antimetabolic Activity*, 1958, p. 258.
[6] Newton, G. G. F., and Abraham, E. P., *Biochem. J.*, 1954, **58**, 103.
[7] Abraham, E. P., and Newton, G. G. F., ibid., 1956, **62**, 658.
[8] —— —— in *Amino Acids and Peptides with Antimetabolic Activity*, 1958, p. 205.
[9] Florey, H. W., *G. Microbiol.*, 1956, **2**, 361.
[10] Abraham, E. P., *Biochemistry of Some Peptide and Steroid Antibiotics*, 1957.

represents a solid and satisfying achievement. Nevertheless, the compound itself is not new. Its total synthesis by J. C. Sheehan and his colleagues in the U.S.A. was reported almost exactly a year ago.[5]

What are the likely contributions of this compound to chemotherapy? Here we are on very uncertain ground. 6-Aminopenicillanic acid itself is a poor antibiotic, but it has potential value as a source of penicillins with new side-chains. Many different penicillins with non-polar side-chains have long been obtainable by the addition of appropriate precursors (almost all of them monosubstituted acetic acids) to the fermentation medium. In general they have not differed markedly from penicillin G in their antibacterial activity, although some of them have shown other properties, such as enhanced stability to acid, which have proved clinically useful. Cephalosporin N, a penicillin with a highly polar side-chain derived from D-α-aminoadipic acid, has a very different range of activity, being more active than penicillin G against certain Gram-negative organisms, in particular the salmonellae, and much less active against Gram-positive organisms.[6] But this substance, obtained from certain species of *Cephalosporium*, is as yet the only example of its type, and its superiority in some respects to the common penicillins has not appeared sufficiently remarkable to compensate for the expense of isolating it on a commercial scale. The chemical acylation of 6-aminopenicillanic acid provides a more versatile route to penicillins with new side-chains than that which is dependent on the enzymic mechanisms of a fungus. It thus offers an opportunity for further exploration in what has hitherto been a somewhat disappointing field.

An unfortunate limitation to the effective use of penicillin arises from the rapid destruction of the substance by the enzyme penicillinase, and the prevalence of penicillinase-producing staphylococci in hospitals has now become a serious clinical problem. The discovery of a modification of the penicillin molecule which would endow the molecule with resistance to the enzyme without greatly affecting its intrinsically high activity and its low toxicity, or which would make it a powerful inhibitor of the action or induction of the enzyme, might thus enable an important advance to be made, at least temporarily, in the treatment of staphylococcal infections. Published work has so far given little encouragement to the hope that this can be done by coupling an appropriate side-chain to the normal penicillin nucleus. One antibiotic has been encountered which is related to the penicillin family and is insensitive to penicillinase; but this substance, cephalosporin C, owes its unusual properties not to a modification in the side-chain (which is identical with that of cephalosporin N), but in the nucleus.[7,8] Although cephalosporin C has a relatively low antibacterial activity, it protects mice, in adequate doses, from infection with a penicillinase-producing strain of *Staph. aureus*.[9] The possibility of obtaining more valuable compounds with a similar nucleus is perhaps not too remote.[10]

Within the next few years we should be able to assess whether any substantial progress in chemotherapy is likely to stem from 6-aminopenicillanic acid. At least one group in the U.S.A. has already had many months to study new synthetic penicillins. The practical significance of the production of the penicillin nucleus by fermentation is mainly an economic one, for the compound may well be obtainable much more cheaply by fermentation than by purely chemical synthesis. In the economic sense the enthusiastic references to a break-through might be justified. But it remains to be seen whether much can be gained from the territory beyond.

A MORAL OBLIGATION

In the House of Lords last week Lord Winterton asked the Government to introduce regulations, or if necessary legislation, to ensure the immediate reinstatement of any consultant or S.H.M.O. whom a court of law holds to have been wrongfully dismissed from his post in the hospital service. Lord Winterton, whose speech is reported in our Parliamentary Notes, referred specifically to the case of Mr. A. H. Barber, who in 1952 was dismissed by the Manchester Regional Hospital Board from his post as consultant obstetrician and gynaecologist at the Oldham and District Hospital. Fifteen months ago Mr. Barber took his case to the High Court. There the judge, finding in his favour, declared that the Minister of Health had acted wrongfully and in breach of his statutory duty in not hearing Mr. Barber's appeal against dismissal, and awarded heavy damages against the board.[1] The B.M.A. thereupon took up the cudgels on Mr. Barber's behalf and sent a deputation to the Minister demanding his reinstatement. As a result of this, though expressing some doubt whether strictly the Barber case fell within clause 16 of the terms and conditions of service of hospital medical staff, the Minister conceded that the Manchester board should act on the basis that it had a "moral obligation" to assist Mr. Barber, and in July so informed the board. Five months later, when questioned in the Commons in

[1] *Brit. med. J.*, 1957, **2**, 1552.
[2] *Hansard*, December 8, 1958.
[3] *The Times*, March 5, 1959.

December,[2] Mr. Walker-Smith said the board had agreed to his suggestion and had accepted this moral obligation. Nevertheless the fact remains that Mr. Barber has still not been reinstated. No wonder *The Times*,[3] in a first leader last week on Lord Winterton's request, headed its blistering attack on the Government "Injustice."

But the "moral obligation" clause goes much further than just one hard case—however hard and however unjust. The clause is written into the terms and conditions of service to which every consultant and S.H.M.O. binds himself when he signs his contract with his regional board. It is his one safeguard against unfair dismissal. Just what is it worth—and is it really workable? The first paragraph of the clause entitles any consultant or S.H.M.O. who thinks his appointment is being unfairly terminated to be heard before a professional committee under the chairmanship of the Ministry's Chief Medical Officer, and obliges the Minister to review the case in the light of this committee's advice. The Minister may then confirm the dismissal, direct reinstatement, or arrange some other solution agreeable to the parties concerned. But in no instance may a board proceed finally to dismiss a consultant or S.H.M.O. unless and until it has received the Minister's agreement. As a last resort there remains, as in the Barber case, appeal to the courts. But, even here, as Mr. Walker-Smith pointed out in Parliament[2] when referring to that case, the court has no power to order reinstatement if the action is successful.

The second paragraph of this vital clause states the conditions where a "moral obligation" exists and defines the nature of this obligation. The paragraph reads: "It is understood that where a local change of organization in the hospital and specialist services involves displacement or serious disturbance of a consultant's (or S.H.M.O.'s) services, the board recognizes that it has a moral obligation to render the greatest possible assistance to the consultant (or S.H.M.O.) with a view to his obtaining comparable work in another hospital." This is not some impossibly rare situation which will never occur. Contraction and expansion as between one specialty and another are bound to happen. The discovery of new remedies can totally alter the deployment of medical effort. The effect of chemotherapy on the tuberculosis service is an obvious example. Again, to-day the cry is for more psychiatrists; perhaps to-morrow many of them will be redundant. And apart from the local effects of such general trends there may also be local maldistributions which in the best interest of the public served should be adjusted. Cases of redundancy are occurring now, though as yet only in small numbers.

What can such people expect? It is not so easy for them to switch in mid-career, to compete with younger men trained perhaps more appropriately for the post offered—even with the benefit of special consideration. The Minister says he has no powers to compel their appointment: it is a matter for the boards. But are the boards themselves, given the best will in the world, much better placed to honour their moral obligation? There may be no suitable vacancy in the region. And, if there is, it must be advertised, and a board can even then appoint only from among those candidates recommended to it by a properly constituted appointments advisory committee. It could happen that such a committee would not choose to recommend a particular redundant consultant or S.H.M.O. Lord Onslow's statement (p. 728) that the advertising rule may now be changed is therefore welcome. It is surely high time to overhaul the machinery and make it more certain. It is to no one's interest to freeze the establishment for each specialty at its present level: Medicine marches on. Equally there must be justice—and reasonable security—for the man who has given years of good service and is then, through no fault of his own, found to be redundant. What comfort to him is a "moral obligation" if there is no job?

OCCUPATIONAL GROUPS

The census held in 1911 contained, for the first time, a number of questions designed to elicit information on the fertility of women. This was a pioneering venture, not repeated until the 1951 census, though just after the second world war a Royal Commission on Population carried out an important inquiry into the population of Great Britain.[1 2] The results of analysing the answers obtained in England and Wales at the 1951 census have now been published in a massive volume,[3] and the hundreds of tables provide data that will be of inestimable value for the analysis of fertility in this country, though it is worth bearing in mind that the forecasting of future trends is apt to be hazardous. It is tempting to project into future years such statistics as have been fairly constant over past years, and it has to be done for the purposes of government, when the risks of doing so have to be taken. One question, often posed, and prompted again by the new figures, is this: What will be the effect on the nation if the differences in fertility between the occupational groups continue for many years into the future? In other words, will the

[1] Report of Royal Commission on Population, 1949. H.M.S.O.
[2] Glass, D. V., and Grebenik, E., *The Trend and Pattern of Fertility in Great Britain*. A Report on the Family Census of 1946. Papers of the Royal Commission on Population, Vol. VI, 1954. H.M.S.O.
[3] *Census 1951, England and Wales, Fertility Report*, 1959. H.M.S.O. (£4 10s.).

inborn qualities that make for outstanding ability decline in average frequency?

In the latest analysis, women are assigned to the occupation of the husband, and these occupations are grouped into the Registrar-General's social classes. Figures showing the average size of family of women aged 45–49 (who have virtually completed their child-bearing) are reported to be as follows:

	Social Class	*Average Family Size*
I	Professional, etc., occupations ..	1.51
II	Intermediate occupations ..	1.62
III	Skilled occupations	1.93
IV	Partly skilled occupations ..	2.36
V	Unskilled occupations	2.64

These figures show a trend similar to that found at the 1911 census, but the report states that average family size in Class I has probably begun to rise. The current fertility of Class I is about equal to the average for all classes, though clearly the figures for a single year may be misleading. (In this context "fertility" refers to children born, not to the ability to bear children, termed "fecundity.") Within the social classes it is the manual workers, particularly unskilled and semi-skilled, who have the largest average size of family, while the smallest families on average are among the clerical, managerial, and professional workers, and traders and shop assistants. On the other hand, the highest infant mortality rate is also among the children born in Class V, and much intermarriage occurs between social classes.

Another pertinent question to ask of data such as these is whether they show that enough babies are being born to maintain the population. Various assumptions have to be made—and the report gives as many as seven estimates on different sets of assumptions. The upshot seems to be that "current habits imply, *in the long run*, approximately full replacement of one generation by the next, and possibly a very little more."

PARA-INFLUENZA

We are all too familiar with the effects of the influenza viruses on man. These viruses are recognized in the laboratory because they grow in chick embryos and agglutinate red cells (haemagglutination). Mumps virus and some animal viruses do likewise, and all are grouped as the myxoviruses.[1] Many influenza viruses will grow in tissue cultures. If red cells are added to the medium, they will stick to any infected culture cells present.[2] This phenomenon has been called haemadsorption. By means of haemadsorption, infection can be detected in a culture when the usual version of the haemagglutination test is negative and when there is no destruction of cells. With the help of this technique workers at the National Institutes of Health, near Washington, D.C., isolated myxoviruses in tissue cultures inoculated with secretions from children in a residential nursery and in hospital.[3] The viruses were not influenzal but belonged to two new serological types which were named haemadsorption virus type 1 and type 2. Infected children developed increasing titres of antibody as measured by tests of haemagglutination inhibition, complement fixation, or neutralization. Now, one year later, these workers report[4] the results of careful studies of over 800 cases of respiratory illness. The patients were mostly under 2 years of age and were seen as hospital in-patients or out-patients. Their illnesses ranged from pneumonia and "croup" to mild afebrile respiratory disease. Over 800 controls were also studied. These resembled the cases in age, sex, economic status, and to some extent in the time of year at which they were seen. Isolation of virus was attempted from all subjects by taking throat swabs and inoculating cultures of monkey kidney cells. Paired sera of 1/3 of the cases and 1/6 of the controls were tested for rising antibody titres. Virus was isolated at most seasons of the year, and from 54 cases and 2 controls in all. Type 1 was isolated from 21 and type 2 from 35 cases. Serological tests told the same story. There were 27% positive results among the cases tested and 7% in the control group. The results indicated that these viruses were almost certainly causing disease. Virus infection occurred in illnesses classified as pneumonia, croup, bronchitis, pharyngitis, and mild febrile or afebrile respiratory disease; this suggests that these viruses may produce, or help to produce, a wide range of clinical syndromes.

The American workers indicate that their investigations were made mainly on the very poor and the very young, and that type 2 virus was apparently absent during a similar study made in Baltimore a year earlier. Furthermore, these viruses have not yet been found in adults, though type 2 virus produced an illness resembling a common cold when given to human volunteers.[5] As both types of haemadsorption virus have now been isolated in Europe[6] we must hope that the relation between these viruses and disease will be studied in fully representative populations both inside and outside the U.S.A. There was evidence that 20% of the children admitted to hospital in Washington with acute respiratory disease were infected with haemadsorption viruses. It remains to be seen if the figure is always so high. Perhaps it is a little early to start classifying these viruses (and their close relatives the Sendai and CA (or ALTB) viruses), but in view of their behaviour in the laboratory and in man there is much to be said for calling them para-influenza viruses.[7] We shall probably hear more of this name in the future.

HEREDITY AND CONGENITAL HEART DISEASE

Congenital abnormalities are becoming more important among the causes of death and disability in childhood, and nowadays parents who have had a child with a defect often ask whether or not another child is likely to be similarly affected. The increasing success of the surgical treatment of congenital heart diseases gives the problem of their causation an added interest, because those who would otherwise have died in childhood may live to reproduce. Thus, if heredity is important, the frequency of the genes responsible may rise in the population.

[1] Andrewes, C. H., Bang, F. B., and Burnet, F. M., *Virology*, 1955, **1**, 176.
[2] Vogel, J., and Shelokov, A., *Science*, 1957, **126**, 358.
[3] Chanock, R. M., *et al.*, *New Engl. J. Med.*, 1958, **258**, 207.
[4] —— *et al.*, *J. Amer. med. Ass.*, 1959, **169**, 548.
[5] Reichelderfer, T. E., *et al.*, *Science*, 1958, **128**, 779.
[6] Sutton, R. N. P., Clarke, S. K. R., and Tyrrell, D. A. J., *Lancet*, 1959, **1**, 395.
[7] Andrewes, C. H., Bang, F. B., Chanock, R. M., and Zhdanov, V., *Virology*, 1959, in press.

It is well established that there is a high frequency of cardiac defects in the children born of women who have had rubella during the first eight weeks of pregnancy.[1 2] It is also well established that the cardiac abnormalities of the rare Marfan's syndrome are determined by the presence of a single dominant gene, even though the heart is not affected in every individual carrying the gene. In the great mass of cases, however, the cause is unknown.

With the exception of maternal rubella, which accounts for only a small proportion of the total number of cases, no environmental factor has ever been convincingly shown to cause congenital heart disease. Other virus diseases in pregnancy have not been incriminated,[1] maternal age does not appear to affect the matter if cases of mongolism are omitted from the sample,[3 4] while opinions are divided on the effect of birth order.[3 5] The suggested relationships of hypoxia[6] and foetal distress[7] to persistent ductus arteriosus have not been established as of general importance.

There are many reports of family pedigrees with more than one affected member, and recently R. A. Carleton and colleagues[8] have collected the reports of 141 such families published since 1941; they have added three more families, two of which each contained three cases of defect of the atrial septum. Maurice Campbell[9] has reported 40 families with two or more cases of congenital heart disease and noted that usually the affected members of a family had the same type of malformation. Though suggestive, this multiple familial occurrence does not prove that the defects have a genetic basis, as a certain number may be expected by chance alone and a whole family may be exposed to some particular environmental cause.

More useful indications of the importance of genetic factors are obtained from surveys of familial incidence, rates of parental consanguinity, and studies of twins. Many workers[2 4 9–11] have reported the incidence of congenital heart disease in the sibs of patients, and it is usually between 1% and 2%. In each series it has been very much higher than the incidence in a control group or than that calculated for the general population. Even so, the frequency is not so high as to suggest that heredity plays an important part. The incidence in the parents of the propositi (i.e., the first children found to have heart disease in each of the families) is not higher than in the parents of the controls. In only one of these series[3] was the amount of parental consanguinity significantly higher in the disease group than in the controls.

I. A. Uchida and R. D. Rowe[12] have investigated 13 uniovular and 13 binovular pairs of twins and in each case only one twin was affected. In another recent series[3] all seven uniovular pairs had only one twin affected, whilst one of the nine binovular pairs had both twins affected. These studies provide further evidence that heredity does not play a very important part in congenital heart disease, and yet they may also be regarded as evidence against intrauterine toxic or infective factors being solely responsible.

The weight of evidence seems to favour both genetic and environmental factors as being the cause of most cases. Perhaps autosomal recessive genes are primarily responsible for the various lesions. They are probably of low penetrance—that is, they may produce the lesions only under the influence of certain environmental factors or under the influence of genes at other loci. Thus the aetiology of these congenital abnormalities may be similar to that of many of the common disorders which develop after birth. Genes of similarly low penetrance probably have a causative role in, for example, duodenal ulcer and cancer, for there is usually no clear-cut pattern of inheritance of these diseases and yet families are occasionally found in which many cases have developed. Recently families have been described[13] in which a single gene has been responsible for many cases of carcinoma of the oesophagus, a neoplasm in which genetic factors are not usually apparent.

Too little is yet known about the aetiology of congenital heart disease for any useful preventive action to be planned, but enough is known about the role of heredity for the physician to reassure parents who have had one affected child that the chances of a second being affected are less than 1 in 50. This is with the proviso that there is no other family history of congenital heart defect, and that the parents are not related. If there is a family history or the parents are related, the chances can be assessed only after examination of many members of the family and genetic analysis of the pedigree.

"GETTING MARRIED"

The fourth edition of the *Family Doctor* booklet "Getting Married," issued last week, contains matter which has caused offence to some sections of the public, and, as letters in this week's *Journal* show, to members of the B.M.A. Two or three telegrams of protest from secretaries of Divisions, letters of a similar nature, and a number of actual and threatened resignations from the B.M.A. because of the booklet, led the Chairman of Council to suspend its further distribution until the Council meets later this month.

As there seems to be some ignorance of the mechanism of this side of the Association's activities, it is well to recall that in 1951 the Council of the B.M.A. appointed a special committee, with special powers, to be responsible for the publication of the monthly popular health journal *Family Doctor*, from which have developed its associated booklets and books, including the one now the focus of controversy.

[1] Hill, A. B., Doll, R., Galloway, T. McL., and Hughes, J. P. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 1.
[2] *Brit. med. J.*, 1958, **2**, 962.
[3] Lamy, M., de Grouchy, J., and Schweisguth, O., *Amer. J. hum. Genet.*, 1957, **9**, 17.
[4] Keith, J. D., Rowe, R. D., and Vlad, P., *Heart Disease in Infancy and Childhood*, 1958, Macmillan, New York.
[5] MacMahon, B., *Brit. J. soc. Med.*, 1952, **6**, 178.
[6] Alzamora, V., *et al.*, *Pediatrics*, 1953, **12**, 259.
[7] Record, R. G., and McKeown, T., *Brit. Heart J.*, 1953, **15**, 376.
[8] Carleton, R. A., Abelmann, W. H., and Hancock, E. W., *New Engl. J. Med.*, 1958, **259**, 1237.
[9] Campbell, M., *Brit. Heart J.*, 1959, **21**, 65.
[10] McKeown, T., MacMahon, B., and Parsons, C. G., ibid., 1953, **15**, 273.
[11] Polani, P. E., and Campbell, M., *Ann. hum. Genet.*, 1955, **19**, 209.
[12] Uchida, I. A., and Rowe, R. D., *Amer. J. hum. Genet.*, 1957, **9**, 133.
[13] Howel-Evans, W., McConnell, R. B., Clarke, C. A., and Sheppard, P. M., *Quart. J. Med.*, 1958, **27**, 413.

Drug Treatment of Disease

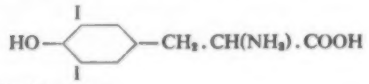
THYROID HORMONES

BY

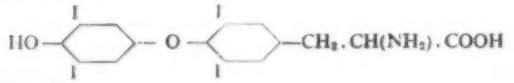
A. W. SPENCE, M.D., F.R.C.P.

Physician in Charge of a Medical Unit, St. Bartholomew's Hospital, London

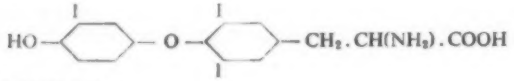
There are two naturally occurring hormones in the thyroid gland—namely, *laevo*-thyroxine (3:5:3′:5′-tetraiodothyronine), isolated by Harington and Salter (1930), and 3:5:3′-*laevo*-triiodothyronine, identified by Gross and Pitt-Rivers (1952). In the biosynthesis of thyroxine, iodide is taken up from the blood and concentrated in the thyroid gland. By enzymatic action iodide is oxidized to iodine, which combines with tyrosine to form monoiodotyrosine and diiodotyrosine. By the oxidative coupling of two molecules of diiodotyrosine, thyroxine is produced. *Laevo*-thyroxine is eight to ten times more active than *dextro*-thyroxine, which does not occur naturally. It is doubtful whether triiodothyronine is formed by the removal of one atom of iodine from thyroxine or by the combination of one molecule of monoiodotyrosine and one molecule of diiodotyrosine (Pitt-Rivers, 1958).



Dilodotyrosine



Thyroxine



Triiodothyronine

Thyroglobulin is the storage protein of the thyroid gland; it is not the thyroid hormone. Incorporated in thyroglobulin are tyrosine, mono- and diiodotyrosines, thyroxine, and a small amount of triiodothyronine. Thyroglobulin does not enter the blood stream, the principal circulating thyroid hormone being thyroxine loosely attached to a protein. Thyroxine and triiodothyronine are released from thyroglobulin by the action of thyroid protease and escape into the blood stream; the iodinated tyrosines are released at the same time, but remain within the gland and are immediately de-iodinated.

Synthetic Hormones

Of the synthetic hormones, mention should be made of the acetic acid analogues of thyroxine and triiodothyronine, in which the alanine side-chain is replaced by acetic acid and which are known as tetraiodothyroacetic acid (tetrac) and triiodothyroacetic acid (triac) respectively; and of tetrabromothyronine and tribromothyronine, in which the iodine of thyroxine in the case of the former compound and of triiodothyronine in the case of the latter is replaced by bromine.

PHARMACOLOGICAL ACTIONS

Thyroxine

The two fundamental actions of thyroxine are (1) the promotion of growth in the young animal, and (2) the stimulation of metabolism. It also controls its own secretion by depressing the output of the pituitary thyroid-stimulating hormone, which is effected when the titre of thyroxine in the blood has risen to a certain level. The hormone is active when given by mouth.

Growth.—Deficiency of thyroxine in the young growing animal causes stunting of growth due to retardation of osseous development. The appearance of ossification nuclei is delayed, and instead of ossification proceeding from one centre in the epiphyses as it does in the normal subject it arises from multiple foci: union of the epiphyses is also delayed. Treatment with thyroxine prevents these disturbances if started sufficiently early. The hormone in excess causes hypertrophy of the heart, liver, spleen, kidneys, pancreas, adrenal glands, gonads, and lymphatic tissues.

Basal Metabolism.—Total thyroidectomy lowers the basal metabolic rate by 40%, and as a result reduces the body temperature. The intravenous injection of a single dose of thyroxine increases the basal metabolic rate after a latent period of six to eight hours, but it does not reach the maximal level until the eighth or tenth day; it then gradually falls and returns to the original level about four weeks after the injection. The causes of the latent period and prolonged action are unknown.

General Metabolism.—Thyroxine stimulates both exogenous and endogenous protein katabolism and in excess causes a negative nitrogen balance. During the period that the basal metabolic rate is rising as a result of the administration of thyroxine creatinuria occurs, but almost disappears when the basal metabolic rate is stabilized at the higher level (Thorn, 1936).

Excessive amounts of thyroxine cause mobilization of glucose in the liver and thus a reduction or disappearance of liver glycogen. Usually glycosuria does not occur because thyroxine increases the utilization of glucose by the tissues. Marine (1935) considered that the depletion of liver glycogen was secondary to the increased utilization of glucose rather than the result of a direct action of thyroxine. The hormone, again in excess, decreases the glycogen content of cardiac muscle, but it produces little change in the glycogen content of the skeletal muscles.

It indirectly causes loss of fat through the increased expenditure of energy and probably also stimulates fat katabolism. It depresses the level of the blood cholesterol.

Excess of thyroxine increases the excretion of calcium and phosphorus in the urine and stools, probably by lowering the renal threshold for calcium, and thus

reduces the level of calcium and phosphorus in the plasma (Robertson, 1942).

Water Balance.—Thyroxine increases the renal excretion of water and salts both in normal and in myxoedematous subjects, the extra fluid excreted probably being derived from intracellular sources in the normal person and from extracellular sources in myxoedema (Byrom, 1934). The increased production of urea through increased protein katabolism may also be partly responsible for the diuresis.

Cardiovascular System.—Thyroxine increases the rate of the heart beat and the cardiac output (1) by a direct action on the heart and (2) indirectly through stimulation of metabolism. As a result of the increased heat production it causes peripheral vasodilatation and sweating.

Other Systems.—The hormone stimulates the mental processes, increases vasomotor activity and thus peristalsis, and maintains the normal texture of the skin and the growth of hair. It stimulates the formation of erythrocytes, but its effect on the leucocytes is variable. Thyroidectomy usually results in a leucopenia with a relative lymphocytosis.

Triiodothyronine

Triiodothyronine is highly active orally and has all the pharmacological properties of thyroxine. It is five time more potent than thyroxine in preventing thiouracil goitre and in promoting the growth of thyroidectomized rats (Gross and Pitt-Rivers, 1953), and is three to four times more potent in the treatment of human myxoedema. The action of triiodothyronine is more rapid and less prolonged than that of thyroxine. Whereas after a single intravenous injection of thyroxine in patients with myxoedema the maximal level of the basal metabolic rate is not reached until the eighth to tenth day, after an equivalent intravenous dose of triiodothyronine the maximal level is attained in 24 to 48 hours and the initial response appears much sooner (Blackburn *et al.*, 1953). In hypothyroid patients treated with triiodothyronine the basal metabolic rate reaches the pre-treatment level in seven to nine days after treatment is stopped, whereas in the case of thyroxine this process occupies several weeks (Lerman, 1953).

Synthetic Hormones

Tetraiodothyroacetic acid (tetrac) and triiodothyroacetic acid (triac) have about one-tenth of the activity of triiodothyronine in preventing thiouracil goitre, and though they cause clinical improvement in human myxoedema their action in raising the basal metabolic rate is rapid and short-lived (Lerman and Pitt-Rivers, 1955). In the treatment of myxoedema tetrac has about one-thirtieth of the potency of thyroxine (Goolden, 1956), and triac is about 75 times less effective than triiodothyronine in depressing the blood cholesterol and in raising the basal metabolic rate (Trotter, 1956).

Tetrabromothyronine is only one-seventeenth as active as thyroxine in myxoedema (Lerman and Harington, 1949), but tribromothyronine has only slightly less thyroid-like activity than has thyroxine (Compston and Pitt-Rivers, 1956), demonstrating that the presence of iodine in a compound is not necessarily essential for the production of a high degree of thyroxine-like action.

THERAPEUTIC USES

There is no indication for the therapeutic use of thyroid hormone in any condition, so far as is known at present, other than hypothyroidism. In the absence of hypothyroidism the administration of thyroid in physiological doses (up to 0.3 mg. of thyroxine daily) will reduce the natural secretion by the amount given by depressing the output of thyrotrophin, and the level of circulating thyroxine will in consequence remain unchanged. Doses in excess of the physiological dose will cause the patient to become thyrotoxic. The preparations advised are tablets of thyroid, *B.P.* (often erroneously called thyroid extract), and *laevo*-thyroxine sodium. 1 gr. (65 mg.) of tablets of thyroid, *B.P.*, is equivalent to 0.1 mg. of *laevo*-thyroxine sodium.

Since thyroxine has a prolonged action its administration three times a day is unnecessary; the total daily dose need be given only once daily, preferably after breakfast. Except when a rapid action is required, as in myxoedema coma, there is no advantage in using the more expensive preparation, *laevo*-triiodothyronine sodium; in fact, its rapidity of action renders its use undesirable in myxoedema and cretinism. Recently it has been claimed that there exists a condition of non-myxoedematous hypometabolism or metabolic insufficiency which is refractory to thyroxine but responds to triiodothyronine, but the evidence so far is not convincing (*British Medical Journal*, 1956; *Lancet*, 1956, 1957).

Cretinism.—As cretins are sometimes hypersensitive to thyroid, the dose at first should be small: for a child aged 6 months, tablets of thyroid, *B.P.*, 1/10 gr. (6.5 mg.) daily, increasing week by week to ¼ to ½ gr. (16–32 mg.). The maintenance dose varies, but at the age of 1 year it is about ½ gr. (32 mg.) and at 4 years 2 gr. (130 mg.). Its administration should be continued for the rest of the patient's life, and the only reason for its interruption is the appearance of symptoms of overdosage. During an infection the dose should be slightly increased.

Myxoedema

Spontaneous Myxoedema.—If treatment is started with the full maintenance dose of thyroid, precordial pain and muscular pains and cramps may arise. This is because the oxygen requirements of the tissues are increased beyond the capabilities of the heart and circulation at this stage to supply them. The daily dose of thyroid should initially be ¼ gr. (32 mg.) and should be increased each week by ¼ gr. (32 mg.) until signs of overdosage, such as tachycardia and irritability, appear. Treatment should then be stopped for two weeks and should be resumed in doses of 1 gr. (65 mg.) a day less than the overdose. The maintenance dose of tablets of thyroid, *B.P.*, varies from 3 to 5 gr. (200–320 mg.) daily. In cold weather the daily dose should be ¼ to 1 gr. (32–65 mg.) higher than in warm weather. The dose should also be slightly increased during pregnancy, during an infection, and temporarily after a surgical operation. *Treatment should not be stopped for any reason apart from overdosage.*

In patients with ischaemic heart disease anginal symptoms may arise before or when the full maintenance dose has been reached. Such patients should be kept hypothyroid, at a level at which angina does not arise. The anaemia of myxoedema disappears with thyroid therapy, but if the condition is complicated by

an iron-deficiency anaemia or by an Addisonian anaemia the appropriate treatment of these diseases should be given in addition.

Post-thyroidectomy Myxoedema. — Myxoedema occasionally arises after subtotal thyroidectomy for toxic goitre. It should be borne in mind that so long as thyroid is given in full doses the secretion of thyrotrophin will be depressed and the thyroid remnants will never hypertrophy. After the hypothyroid symptoms have been controlled with thyroid therapy an endeavour should be made to see whether treatment can be withdrawn. The daily dose of thyroid should be reduced by ½ gr. (32 mg.) each week ; this procedure gradually lifts suppression of thyrotrophin and gives the thyroid remnants a chance to hypertrophy. It may or may not be successful.

Myxoedema Coma.—The cause of myxoedema coma is usually inadequate dosage of thyroid during very cold weather, but occasionally it is an infection. On account of its rapidity of action *laevo*-triiodothyronine sodium seems to be the preparation of choice, but because the condition is rare the correct dose is uncertain. Suggested doses are 0.1 to 0.25 mg. injected intravenously every 12 or 24 hours until the patient comes out of coma. This treatment should be supported by endeavouring to raise the body temperature gradually by means of an electric blanket, and, if an infection is suspected, by the administration of penicillin. The intravenous administration of fluids is contraindicated because in this disease there is fluid retention.

Masked Hypothyroidism.—Mild hypothyroidism may present as anaemia, constipation, debility, menorrhagia, amenorrhoea, or climacteric symptoms, and patients with these conditions, when due to hypothyroidism, are benefited by thyroid in doses of 1 or 2 gr. (65 or 130 mg.) daily.

Hypopituitarism.—Hypothyroidism secondary to hypopituitarism is treated on the same lines as spontaneous myxoedema.

Simple Goitre.—Simple goitre is an expression of hypothyroidism. Diffuse goitres may be treated with thyroid, which may cause reduction in their size or even their disappearance, but nodular goitres do not usually respond. The rationale is to inhibit the secretion of thyrotrophin, which is directly responsible for the glandular enlargement. Tablets of thyroid, *B.P.*, are given at first in daily doses of 1 gr. (65 mg.) ; each week the daily dose is increased by ½ gr. (32 mg.) to tolerance, the ultimate dose being 3 to 5 gr. (200–320 mg.). If no reduction in the size of the goitre is observed after a few months the treatment should be abandoned, but otherwise it should be continued, the maximal effect being obtained after at least a year. Recurrence may be prevented by the taking of 2 or 3 drops of Lugol's solution every fortnight.

Thyroid therapy may be employed for a few months before the removal of a restrosternal goitre in an effort to reduce its size and thus facilitate the surgical procedures.

Obesity.—Thyroid hormone is not advocated for obesity unless the condition is due to hypothyroidism.

REFERENCES

Blackburn, C. M., McConahey, W. M., Keating, F. J., Jr., and Albert, A. (1953). *J. clin. Endocr.*, **13**, 852.
Brit. med. J., 1956, **2**, 702.
Byrom, F. B. (1934). *Clin. Sci.*, **1**, 273.
Compston, N., and Pitt-Rivers, Rosalind (1956). *Lancet*, **1**, 22.
Goolden, A. W. G. (1956). Ibid., **1**, 890.
Gross, J., and Pitt-Rivers, Rosalind (1952). Ibid., **1**, 439.
—— —— (1953). Quoted by Pitt-Rivers, R. (1953). *Mem. Soc. Endocr.*, No. 1, p. 11.
Harington, C. R., and Salter, W. T. (1930). *Biochem. J.*, **24**, 456.
Lancet, 1956, **2**, 826.
—— 1957, **2**, 992.
Lerman, J. (1953). *J. clin. Endocr.*, **13**, 1341.
—— and Harington, C. R. (1949). Ibid., **9**, 1099.
—— and Pitt-Rivers, Rosalind (1955). Ibid., **15**, 653.
Marine, D. (1935). *J. Amer. med. Ass.*, **104**, 2250
Pitt-Rivers, Rosalind (1958). In *Modern Trends in Endocrinology*, edit. by H. Gardiner-Hill, p. 3. Butterworth, London.
Robertson, J. D. (1942). *Lancet*, **2**, 672.
Thorn, G. W. (1936). *Endocrinology*, **20**, 628.
Trotter, W. R. (1956). *Lancet*, **1**, 885.

ASSESSMENT OF THE RESULTS OF FIVE YEARS OF CANCER EDUCATION

BY

JEAN AITKEN-SWAN, A.M.I.A., A.H.A.

AND

RALSTON PATERSON, C.B.E., *M.C.*, M.D., F.R.C.S. F.F.R.

Christie Hospital and Holt Radium Institute, Manchester

During the past five years an intensive campaign of cancer education has been carried out by the Manchester Committee on Cancer in a defined "experimental" area with a population of just over 600,000. Its object was "to test the effect of saturating a defined area with intensive propaganda of every suitable kind, to develop propaganda techniques, and to assess effects on the lay public" (Paterson *et al.*, 1954). A "control" area of similar population structure was also defined in which no planned education took place.

Previous investigations had drawn attention to two facts: (1) how widespread was the belief that cancer is never cured (Paterson and Aitken-Swan, 1954); and (2) that where cancer is suspected fear is a potent cause of delay in seeking treatment (Aitken-Swan and Paterson, 1955).

The main effort of the campaign in the experimental area was therefore directed towards encouraging realization that some types of cancer are in fact curable. Attention was centred primarily on cancers of the breast and cervix uteri.

The first attempt at objective assessment of the impact of this campaign was through surveys of public opinion, contrasting experimental with control areas (Paterson and Aitken-Swan, 1958). The present article describes three further attempts at evaluation from other angles.

1. *A retrospective study of patients' delay in seeking advice.* The delay of patients with breast or cervix cancer whose symptoms were first noticed during the years before any education had taken place is compared with the delay of those whose symptoms were first noticed in the years during which education had been going on.

2. *Analysis of staging.*—Changes are analysed in the proportion of cases referred to this hospital between 1950 and 1956 presenting with growths of limited extent (often referred to as "early").

3. *An interviewing inquiry.*—New patients with breast or cervix cancer, resident in the experimental area and registered at this hospital between 1953 and 1957, were interviewed to find out indirectly if they were aware that cancer education was going on and if it played any part in their coming under medical care.

In presenting results after such a short period as five years (three years for the delay index) it is realized that the campaign could only have started to make a measurable impact on the area. Nevertheless, the first five years' work had been planned as an experiment, in regard both to the running of the campaign and to the methods of assessing its effects. An interim report at this stage therefore seemed indicated.

A Retrospective Study of Patients' Delay in Seeking Advice

One obvious index of impact of the education would be a demonstrable shortening, for at least some patients, of the period of delay in seeking advice. Delay, defined as the interval between the first symptom and first consulting a doctor, was analysed in this study by year of onset of symptoms and not by year of presenting at hospital. The population analysed, which we will call the "Christie Hospital series," can be defined as all patients registered at this hospital with breast or cervix cancer, resident in the experimental or control areas, whose symptoms were first noticed during the years 1950–5 inclusive, and where the interval between onset of symptoms and treatment was up to two years after the date of onset. This last qualification had to be added for statistical reasons in order to avoid the anomaly of having to add cases for an indefinite period if the final years of the series were to be fairly contrasted with the earlier. It was also not possible to achieve the ideal of ascertaining the necessary facts from all such patients in the two areas.

Although the great majority of patients with breast and cervix cancer in this region are sooner or later referred to the Christie Hospital a check made at the experimental area hospitals (through the courtesy of the surgeons concerned) showed that for the six years 244 patients with breast cancer and 52 with cervix cancer were treated at hospitals in that area and not yet referred to the Christie Hospital. A similar number can be presumed for the control area. The delay of this group could not be included in our statistics as these hospitals did not as a rule record the necessary data. It is important to note, however, that if in the experimental area the campaign did in fact induce more patients to seek advice earlier these would be the very cases which tended to be taken for surgery without radiotherapy, and the Christie Hospital series taken by itself therefore provides a minimum estimate of the impact of the campaign. Table I shows the numbers analysed.

TABLE I.—*Christie Hospital Series: Numbers Analysed*

Site	Area	Total	Excluded Because:		No. Analysed
			Delay Over 2 Years	Year of Onset Not Known	
Breast	Experimental	810	43	24	743
	Control	787	37	60	690
Cervix	Experimental	313	4	8	301
	Control	258	7	7	244

Results are shown (Table II) in three two-year periods equivalent to the pre-campaign (1950–1), intermediate (1952–3), and campaign years (1954–5). Because of the two-year lag on this type of analysis the latest figures measure effect only up to about the third (and not the fifth) year of active education.

TABLE II.—*Patients' Delay by Year of Onset Expressed as Percentage of Total Cases*

Patients' Delay	Experimental Area			Control Area		
	1950–1	1952–3	1954–5	1950–1	1952–3	1954–5
Breast Cancer						
Total No.:	215	272	256	226	230	234
Under 1 month (immediate action)	28%	33%	38%	32%	28%	31%
1 under 3 months	21%	19%	18%	19%	24%	19%
3 ,, 12 ,,	30%	28%	28%	30%	34%	31%
12 to 24 ,,	16%	18%	15%	15%	10%	16%
Not known	4%	2%	1%	4%	3%	3%
Cervix Cancer						
Total No.:	102	109	90	97	75	72
Under 1 month (immediate action)	37%	43%	39%	29%	32%	24%
1 under 3 months	20%	20%	20%	22%	13%	12%
3 ,, 12 ,,	28%	28%	30%	37%	39%	35%
12 to 24 ,,	8%	5%	7%	6%	11%	6%
Not known	7%	4%	4%	6%	5%	24%

The results for breast cancer show that in the experimental area there has been a steady increase over the years in the proportion of women seeking advice in *under one month.* The difference between the proportions in the pre-campaign and campaign years is very nearly statistically significant at conventional 1:20 levels ($\chi^2=3.47$, $p=0.06$). Nearly all the patients making up the 38% in 1954–5 were interviewed, showing that in 6% of these cases patients actually attributed their "immediate action" to the campaign. No such improvement is seen in the control area. This definite change in the immediate-action group in the experimental area would appear to be the key effect of the education, and all other figures show remarkable stability.

Results for cervix cancer are difficult to interpret because the numbers are small and the proportion in the control area in 1954–5 in which patients' delay was not known was high. It may well be that this method of assessment falls down with cervix cancer because of the real difficulty of determining the date of first symptom. Evaluation from another angle is attempted in the next section, which examines the stage of disease when first seen, and in the interviewing inquiry.

Changes in Stage of Disease When First Seen

The second possible index of effectiveness of any public education would be clear evidence that a higher proportion of cases were presenting with growths of limited extent (the so-called early). Various analyses

TABLE III.—*Cases Presenting in Stages 1 and 2*

Site	Area	1950–2		1954–6	
		Total	%	Total	%
Breast	Experimental	321	55	391	64
	Control	306	67	343	64
Cervix	Experimental	174	50	146	70
	Control	144	52	128	53

were therefore made of the proportion of cases referred to the hospital over the period 1950 to 1956 in stages 1 and 2—for cervix cancer (international staging) and breast cancer (Manchester staging). Unfortunately, for the small units of population involved the numbers per year available for this type of contrast were such that random variation was considerable, and although a general trend seemed apparent it was not definite

enough for any dependable analytical study on a year-to-year basis. Nevertheless, the overall picture gives some indication of a possible effect, especially for cervix cancer (Table III).

Interviewing Inquiry

This inquiry was made amongst patients with breast and cervix cancer resident in the experimental area and registered at this hospital between January, 1953, and December, 1957—the population "at risk" of having come into contact with the education campaign. Those who made only one attendance or who were too ill, too deaf, or mentally unfit were omitted. Results are based on 603 (87%) of the 697 patients with breast cancer, and 221 (82%) of the 269 with cervix cancer eligible for interview. During a conversation ostensibly centred on the medical history it was hoped to learn indirectly what had caused the patient to seek advice when she did and if she was aware of the existence of the campaign. Many of the interviews were recorded, always with the patient's knowledge.

Table IV shows for each year since the interviewing study began the number of patients aware of the existence of the campaign either through hearsay or personal contact, and, separately, the number in personal contact with it *before* they had sought advice. Except where otherwise stated subsequent analyses refer to this second group of 244 cases (34% of the breast cases interviewed plus 18% of the cervix cases).

TABLE IV.—*Knowledge of Campaign*

Site	Year of Registration	Total Interviewed	Aware of Campaign	In Personal Contact with Campaign
		No.	%	%
Breast	1953	102	46	23
	1954	138	42	24
	1955	130	64	42
	1956	125	55	39
	1957	108	55	41
	All years	603	53	34
Cervix	1953	45	7	0
	1954	47	23	15
	1955	36	39	22
	1956	46	28	24
	1957	47	38	30
	All years	221	27	18

TABLE V.—*Type of Propaganda and Numbers Influenced*

Site	Year of Registration	Talks		Articles Only	
		Attended	Influenced	Read	Influenced
Breast	1953	2	2	21	9
	1954	7	6	26	5
	1955	9	7	46	16
	1956	8	4	41	13
	1957	13	5	31	9
	All years	39	24	165	52
Cervix	1953	0	0	0	0
	1954	0	0	7	1
	1955	2	1	6	2
	1956	0	0	11	1
	1957	3	0	11	0
	All years	5	1	35	4

Table IV shows that the campaign has become increasingly widely known over the years, the rate of increase being most marked for cervix cancer. One striking feature of the table, difficult to interpret, is the difference between the figures for breast and cervix cancer. Although each group should be a random selection from the whole area, many more women with breast cancer knew of the campaign or had come into contact with it.

The type of propaganda remembered by the patients and the numbers who considered themselves influenced by it to seek advice are shown in Table V.

The "influence" of the campaign can be assessed only by what can be learnt from the patient. She did not know that the interviewer was specially interested in this aspect, and there seems no reason to suppose it could have any emotional connotations for her. It seems reasonable, therefore, to accept the patient's statement on this, but it should be noted that the group entered as "influenced" contains only those who were consciously aware of having been influenced. In Table V 20 patients who had both attended talks and read articles are included under "Talks," as analysis shows that this was the main influential factor. Out of the 44 who had attended a talk 25 (57%) had been stimulated to take action, compared with 56 (28%) out of the 200 who had only read articles. Again there is a marked difference between results for breast and cervix cancer. About three times as many patients with breast cancer as with cervix cancer claim to have been influenced by propaganda (37% compared with 12%).

The 1957 survey of public opinion in the experimental area (Paterson and Aitken-Swan, 1958) provided an opportunity of ascertaining how many women in a random sample of 1,180 had heard of talks or had read articles about cancer in the local papers. Table VI contrasts this proportion with the proportion amongst the 155 patients (108 with breast cancer and 47 with cervix cancer) interviewed in 1957 (see Table IV).

TABLE VI.—*Knowledge of the Campaign in Patients and Non-patients*

	Patients with Breast or Cervix Cancer, Experimental Area, 1957	Non-patients, Opinion Survey, Experimental Area, 1957
Total No.	155	1,180
Heard of talks on cancer	28%	8%
Attended talk(s)	12%	4%
Read or saw articles in local papers	35%	39%

TABLE VII.—*Patients in Contact with the Campaign. Analysis of Those Not Influenced by it to Seek Advice*

	Breast	Cervix
(Influenced by campaign)	76	5
Not influenced by campaign:		
Too afraid to take action or dismissed the matter from their minds	69	12
Ignorance that their symptoms had any connexion with what they had read or heard	11	8
Vague about what exactly they had read or heard	9	12
Would have gone to the doctor promptly anyway, did not need to be told	14	0
Fatalistic acceptance—"too old to bother"	5	0
Other, emergency, condition found by doctor, etc.	20	3
Total in contact with the campaign	204	40

The reasons for classifying patients who had attended talks or read articles as not having been influenced by the campaign are set out in Table VII.

The following quotations from recorded interviews illustrate some of these categories.

Patients Classified as having been Influenced by the Campaign to Seek Advice

1. Aged 52; no delay; breast cancer. This patient mentioned the campaign in her opening sentence. She went to her doctor promptly because of a talk given to her

ladies' church group. "It took all our fear away. It seems an odd thing to say people enjoyed a talk on cancer; but yes, they were very interested." She described the talk in detail.

2. Aged 47; 5 months' delay; cervix cancer. "I've read bits in the *Chronicle* about if you have bleeding after the change to see your doctor, and I thought this might apply to me. I wrote to Nurse Drew of the *Women's Own* for a booklet about the change, and it also said if bleeding continues after the change to see the doctor, so I thought I would at the first opportunity."

Patients Classified as not having been Influenced by the Campaign

3. Age 72; 6 months' delay; breast cancer. "I thought the article just applied to my case, but I dismissed it." She read a second article and "was impressed" but still did nothing.

4. Age 66; 4 months' delay; breast cancer. "When I read that article in the *Morning News* I said, Hullo, that's for me. But I didn't bother. It didn't frighten me—I know I should have gone sooner. I did believe what it said in a way, but I didn't want to interfere with their (the family's) holidays."

Two final longer quotations show clearly the prevalent attitude to cancer and the problems which face cancer education.

5. Aged 66; 8 years' delay; breast cancer. This patient said she had read articles in the local paper. "And then I went to two lectures that two doctors gave about lumps in the breast. But it never convinced me it were anything serious. I thought when I helped with tea and biscuits little did they know, talking to them afterwards, that I had a secret." "*Their talks didn't encourage you to tell your doctor about it?*" "Not a bit. It didn't alter things one bit. I didn't think the lump was doing me any harm or any danger, and I had had so much with my hip and my knee that I just thought I'd had enough." This patient had also been alarmed by stories from others. "She kept saying, 'Don't bother about it,' and then I had another friend and she wouldn't go for treatment and of course she died." "*What was she frightened of?*" "I don't think she was frightened of anything, but she didn't believe in operations—that's all I could get from her."

6. Aged 51; 4 years' delay; breast cancer. This patient spoke as if mystified by her behaviour. "I hung on and hung on," she said. "Of course, I know it was very wrong, but I don't think there's anyone that comes if they don't say anything right away, you know." About the articles she had read she said: "I used to read anything like that. I used to think to myself, well—I've always had faith, even when my husband was ill in hospital I never lost faith, and even with this I used to think it may be or it may not be; I don't know. And of course, as I say, if there's anything about it in the papers I always read it." "*It didn't encourage you to tell your doctor about it, did it?*" "I don't think that it did. Well, I used to feel sorry, you know; I used to think, 'Well, there's thousands of people like that.' I don't know if I'm the same or not. I kept wanting to go, but you know I kept holding back; I don't know why really."

The "Immediate Action" Group

Finally, the interviewing inquiry provided an opportunity of investigating the responsibility of the campaign in those cases where immediate action had been taken. Out of the 824 interviewed patients registered here between 1953 and 1957, 295 had sought advice in under one month. The check showed that 73 of these had been in personal contact with the campaign, a further 32 knew of it through hearsay, and the remaining 190 had never heard of it. What appeared to be the main factor in bringing these 295 patients under medical care is shown in Table VIII.

TABLE VIII.—*Patients who Took Immediate Action: Main Factor Bringing Them Under Medical Care*

	Breast	Cervix
Finding the symptom	100	31
Education campaign	36	2
Advice or insistence of friends	27	11
Severity of symptoms; emergency	7	21
Under doctor already; doctor calling to see someone else	21	16
Other cancer propaganda	8	1
Reading a "medical book"	4	2
Other, condition found by doctor, etc.	8	0
	211	84

It is difficult to analyse further the first group of 131 without a greater knowledge of personal factors. Twenty-five of them had read articles or had heard talks, but did not consider that this was what had influenced them. Patients with breast cancer described their reactions in such words as: "I'm not the sort who could delay." "I honestly don't think that reading anything influenced me one way or the other. I just couldn't have ignored what was obviously there." "I went because I knew it shouldn't be there and I wanted to get my mind put at rest."

Those with cervix cancer did not seem to have this sense of urgency, and often expected "a bottle" would put them right. More patients with cervix cancer than with breast cancer were in ill-health and under the care of their doctors at the time of onset of the cancer symptoms. Thirty-six with breast cancer and two with cervix cancer directly attributed their promptness to the campaign. This is 5% of the total 824 patients interviewed, and a direct measure of minimum success. The campaign may also have influenced patients through friends whose advice or insistence was the "cause" of their seeking advice at once, or in other indirect ways.

Further analysis of this small group of 38 motivated by the campaign to seek advice in under one month shows that all but five presented at hospital with growths in an "early" stage. It also shows that in 10 of the 38 cases there was a delay of two months or more *after* they had consulted a doctor—either medical or waiting-list delay or due to the patient failing to return after having been reassured.

Discussion

This picture of the effect of the educational campaign at three years (for the delay study) and five years (for the interviewing study) should be read in conjunction with the previously published survey of public opinion on cancer (Paterson and Aitken-Swan, 1958). Three points seem to stand out: (1) that a change in opinion and action can in fact be demonstrated by these methods, at least for breast cancer, after such a short period as three years of education; (2) that the change is extremely gradual; and (3) that the change is effected through a minority of the women reached.

On the objective factual side the following findings seem to have been established.

1. An improvement has been achieved in the experimental area in the proportion of patients with breast cancer seeking advice in under one month (Table II), and the campaign has been shown to be responsible for this.

2. There is some, albeit rather thin, evidence for both breast and cervix cancer that the proportion of cases coming with growths of limited extent has increased more in the experimental than in the control area. This is in interesting contrast to the absence of any improvement in the delay figures for cervix cancer.

3. There is a clearly demonstrated difference between patients with breast and with cervix cancer in their knowledge of, and response to, the campaign.

4. Three times as many patients (in the present study) as non-patients (in the survey of public opinion) had attended talks on cancer, although the talks were given at the regular meetings of women's societies and not at public meetings. This suggests, as does the previous point, that, to some extent at least, cancer talks attract those who have a personal concern with cancer.

5. So far as method of education goes, the informal talks at women's meetings are more effective but reach a smaller fraction of people than newspapers and other printed publicity.

These facts can be interpreted in many ways, and such interpretation must be to some extent speculative. The curious breast/cervix differences are almost certainly bound up with the fact that a painless lump in the breast is already widely feared to be cancer while the significance of the early signs of cervix cancer is less well appreciated.

The need in breast cancer is to diminish fear, and that ignorance is not the only or even the more challenging factor is plain from Table VII. Of all the patients in contact with the campaign, one-third were still too afraid to act upon advice received. The extracts given from interviews with some of these patients illustrate the difficulties of this type of problem. In contrast it may well be that the need in cervix cancer is to establish recognition of significant symptoms in some way or other, yet without inducing fear. On the other hand, improvement here may flow rather from an overall improved attitude to "doctoring" and an increased willingness to seek advice for all abnormal or disturbing symptoms. The doctor's action when such advice is sought is often as great a determinant of the outcome as anything the patient with cervix cancer may do, perhaps even a greater.

The low indices of impact shown by the interviewing inquiry may seem at first disappointing. In measuring effects of the campaign upon patients with proved cancer we are excluding from consideration the unknown number of women motivated by the campaign to have their breast lumps or unusual bleeding investigated. The standard of success—the number of women who were consciously aware of having been influenced by the campaign to seek advice within one month and whose condition proved to be cancer of the breast or cervix—is a stringent one, and it is not surprising if changes over such a short period as three to five years are small. It may well be that a much longer period of education has to be faced up to before substantial results can be expected. Much of this, as the opinion survey showed, depends not on effects upon individuals but in changing the whole climate of public opinion towards cancer so that rational action becomes accepted as natural. This idea must not be taken too far, however, as was shown by the difference already mentioned between patients' and non-patients' readiness to attend cancer lectures (Table VI).

These speculations raise the question of whether the emphasis on "saturation" of the educational area is the right one. This means depth rather than wide coverage, and yet results suggest that many will continue to resist being convinced. Whether repetition would make them more receptive is open to question—some examples quoted suggest that it would not. On the other hand, a minority can be stimulated to act if they are given suitable information at the right moment. It might prove of more value, therefore, to see that sustained education reaches a wide population so that this minority may be as numerous as possible. They in turn become able to influence their relatives and friends—perhaps more effectively than formal lay education—should need arise. Analysis of the total cases has shown that the advice and persuasion of friends is the second most important factor bringing patients under medical care.

Summary

After three years of intensive cancer education in a defined experimental area the proportion of women with breast cancer seeking advice in under one month had risen from 28 to 38%. No such change is seen in a comparable control area where no planned cancer education had taken place. The comparable figures for cervix cancer suggest that delay has remained largely unaltered since pre-campaign years and between the experimental and control areas, but the statistical material is less reliable.

Analysis by stage of disease shows some increase in the five years in the experimental area in the proportion of patients, both those with breast and those with cervix cancer, presenting with growths of limited extent.

Interviewing of patients confirms that the campaign is making more impact on patients with breast than on those with cervix cancer. After five years of education 34% with breast cancer had come into contact with the campaign, compared with 18% with cervix cancer. Of those in contact, 37% and 12% respectively had been influenced by it to seek advice. Of the 244 patients in contact with the campaign, one-third were too afraid to act upon the advice given. Talks were more influential than articles but reached a smaller public.

REFERENCES

Aitken-Swan, J., and Paterson, R. (1955). *Brit. med. J.*, **1**, 623.
Paterson, R., and Aitken-Swan, J. (1954). *Lancet*, **2**, 857.
—— —— (1958). Ibid., **2**, 791.
—— Brown, C. M., and Wakefield, J. (1954). *Brit. med. J.*, **2**, 1219.

A recent statement from the National Academy of Sciences-National Research Council of the U.S.A. comments briefly on the problem of a relationship between leukaemia and radiation. Its comments are made on the *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation* (1958), and are as follows: "The question of induction of leukaemia or other types of cancer in man by very small doses of radiation has been treated in the United Nations report to suggest that the hypotheses of linearity and threshold effects as applied to the behaviour of somatic cells have equal likelihood of validity. Our committee inclines to the view that many forms of cancer, including leukaemia, arise through a more or less complex series of responses. While somatic mutations may be included among these, it seems doubtful that a strict linearity analogous to that seen in the genetic effects of radiation is as likely to hold in the case of these conditions. We note also that there is a considerable body of experimental evidence favouring non-linearity in specific instances. Also, the report seems largely to emphasize the two extreme possibilities, that of a linear relation and of a threshold, and gives little attention to non-linear relations. It is recognized that large-scale definitive experiments and demographic observations are needed since they may be of help in resolving these questions."

Reports of Societies

HEBERDEN SOCIETY

A meeting of the Heberden Society was held at the London Hospital on February 27.

Mr. O. J. VAUGHAN-JACKSON described attrition rupture of the extensor tendons in rheumatoid arthritis. The clinical picture was both common and uniform. The little-finger tendon was the first to go, and the other tendons then ruptured seriatim—ring, middle, index—in that order. Prompt exploration always revealed a hole in the distal tendon compartment over the lower end of the ulna, through which a bony spicule abraded the tendon. Sometimes the tendon ends were joined by a thin tube of peritendon within which the severed ends had retracted. Removal of the lower end of the ulna and grafting the tendons restored normal function. Similar ruptures of flexor tendons might occur. Tendon ruptures caused more deformity than had hitherto been recognized and were unusual among rheumatoid lesions in being reparable.

Dr. W. WENLEY described an experiment in which 10 female beds previously used for the treatment of skeletal tuberculosis at Black Notley Sanatorium had become available as a result of a regional rheumatism scheme. Forty patients with severe and long-standing rheumatoid arthritis had been treated for an average of 6½ months with prolonged bed rest, as much out of doors as possible, and with suitable splinting. Other treatments had been much restricted. By the time of discharge the proportion only partially disabled had increased from 50 to 68% and the completely incapacitated group had decreased from 50 to 24%, with further improvement after discharge. Severe incapacity appeared to be no contraindication to admission to a sanatorium regime. Dr. J. J. R. DUTHIE in the subsequent discussion reported that he had used complete body splintage for up to a month in patients with rheumatoid arthritis. Ankylosis did not occur and there was considerable improvement in the disease.

Dr. D. GREENBAUM had studied renal function and renal biopsies in 13 patients with gout, three of whom were suffering from obvious renal disease with uraemia. Of the remaining ten, who appeared to be healthy apart from their gout, eight had moderately abnormal renal function tests and in eight the renal biopsy showed a slight increase in interstitial fibrous tissue. Uric acid or urates could not be demonstrated in the biopsy specimens. In a further eight kidneys from gouty patients examined post mortem, seven of which were histologically abnormal, uric acid was found in only two. Renal biopsy in these patients had thrown no further light on renal damage in gout, although completely normal kidneys, as shown by histological appearance and function tests, were not found in any of the patients.

Other papers were read by Dr. R. M. MASON, Dr. R. D. CATTERALL, and Dr. V. L. STEINBERG.

ROYAL SOCIETY OF TROPICAL MEDICINE

At a meeting of the Royal Society of Tropical Medicine and Hygiene on February 19, Professor K. R. HILL, formerly professor of pathology in Jamaica, discussed liver disease in the West Indies. He commented on the relative infrequency of hepatic cirrhosis and primary hepatic carcinoma there, which raises the question whether the fatty liver of kwashiorkor leads to cirrhosis.

Hepatic veno-occlusive disease, Professor Hill stated, was seen predominantly in children, aged 1 to 5 years, who were significantly underweight and had a marked background of malnutrition. The essential finding in the acute stage of the disease was blockage of the medium-sized and smaller hepatic veins by a subendothelial swelling of the intimal tissues. It was apparently due to oedema but later became collagenous. The intimal occlusion produced a centrilobular block with distension of the tributary sinusoids. The condition was thought to be caused by the ingestion of "bush teas" or other food containing the pyrrolizidine group of alkaloids which are found in the plants of genus *Senecio* and *Crotalaria*. Recently Dr. C. F. Stephenson, in Professor Hill's laboratory at the Royal Free Hospital, had produced veno-occlusive disease in rats by the intraperitoneal injection of monocrotaline, a substance isolated from several species of *Crotalaria*.

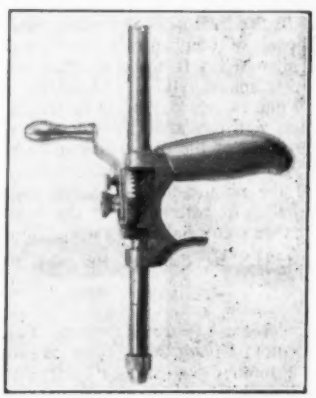
With regard to the vomiting sickness of Jamaica, Professor Hill said necropsy always showed marked fatty metamorphosis of the liver and fatty changes in other organs such as the kidney and heart. Hypoglycaemia invariably accompanied the sickness, and the vomiting was relieved and the patient's condition dramatically improved by intravenous glucose. Recent work in Jamaica strongly supported the conclusions, earlier reached by Sir Harold Scott, that consumption of unripe ackees was the cause of the condition. Professor C. H. Hassall, in Jamaica, had recently isolated from ackees two compounds, named hypoglycin A and B, which in animals caused severe hypoglycaemia, depletion of liver glycogen, and death.

In the discussion, Dr. J. H. WALTERS suggested that the low incidence of cirrhosis in Jamaica, compared with tropical Africa, might be due to Jamaica's relative freedom from malaria. Professor A. W. WOODRUFF said that in animals, if as much as 15% of the liver was replaced by fat, cirrhosis was likely to follow, but less severely affected livers might recover completely.

New Appliances

THE REIDY LIGHT-WEIGHT HAND-POWERED DRILL

Mr. J. P. REIDY, consultant plastic surgeon, Westminster Hospital, writes: The present standard patterns of bone drills are heavy and too unwieldy for the usual plastic bone procedures. I have devised a drill which is light, strong, well balanced, and fitted with a pistol-type grip which gives more accurate one-handed control. The drill (see illustration) is fitted with a small hand-driving wheel with variable position for the crank, or the drive-wheel can be removed so that the drill can be connected to the ordinary mobile dental engine flexible drive. The chuck is small, but is supplied with three collets of different sizes to allow drills up to 3/32 in. (2.4 mm.) to be used. In addition, the shaft of the drill is hollow to allow for the use of Kirschner wires.



This instrument has been produced for me by Messrs. Allen & Hanburys Ltd., Bethnal Green, London, E.2.

A fourth edition of Chauncey D. Leake's translation of William Harvey's *De Motu Cordis* has been published by Charles C. Thomas, Springfield, Ill. This translation, based originally on the Longhine edition of 1697, is freely annotated and includes some illustrations and a chronology of Harvey, but is without the facsimile of the original Latin edition which accompanied Dr. Leake's first edition (1928). It is available in this country from Blackwell Scientific Publications, Oxford (pp. 150+xxiii; 9 plates. 20s.).

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Marcoumar (Roche Products).—This synthetic anticoagulant is a coumarin derivative, its chemical formula being 3-(1'phenyl-propyl)-4-hydroxycoumarin. It is available in tablets of 3 mg. for oral administration.

There have been a number of clinical trials of marcoumar over the past five years. It is relatively rapid-acting and produces a fall in prothrombin level after 24 hours, but the full therapeutic effect is not usually reached until the second, third, or fourth day with normal dosage (5 to 7 tablets on the first day, 3 to 4 on the second, and ½ to 1½ tablets thereafter). Maintenance of a satisfactory prothrombin value over a considerable period is possible, with little variation required in the daily dose. For safe control of dosage, prothrombin estimations should be carried out at weekly intervals. Haemorrhagic complications are infrequent, provided therapy is carefully controlled. Should these occur, vitamin K should be given, and in severe haemorrhage it may be necessary to give transfusions of whole blood. The general indications for and contraindications to the use of marcoumar are the same as for other anticoagulants.

N.H.S. basic price: 25 tabs. 3 mg., 5s.

Disipal (Camden Chemical Company).—This substance is chemically related to diphenhydramine hydrochloride ("benadryl") and is known as orphenadrine hydrochloride, a hydrogen atom being replaced by a phenyl group. It was originally introduced as an antihistamine, later used against motion sickness, and then found to be an active spasmolytic. It has now been well tried in the reduction of rigidity in Parkinsonism, which is its greatest value. It has also been used with limited success in psychiatry in association with reserpine.

In the treatment of Parkinsonism its effects are similar to those of diphenhydramine and benzhexol ("artane," "pipanol"). It is useful either alone or in conjunction with other spasmolytics. The tablets are of 50 mg., a dose of 50 mg. twice a day being increased slowly to 8 tablets a day. It is well tolerated, the side-effects being minor and similar to those of the other substances given for the treatment of Parkinsonism, particularly dryness of the mouth, dilatation of the pupils, and abdominal discomfort. It may also be tried as an alternative to the many other spasmolytics if a change seems indicated through intolerance or ineffectiveness.

N.H.S. basic price: 100 tabs. 50 mg., 13s. 10½d.

Refagan (Farbenfabriken Bayer (Distributors: Levmedic)).—Each tablet contains salicylamide 2 g., phenacetin 2 g., anhydrous caffeine 0.05 g., incidal (5-benzyl-1:2:3:4-tetrahydro-2-methyl-γ-carboline hydrogen naphthalene-1:5-disulphonate) 0.015 g. These tablets have an analgesic and antipyretic action because of the phenacetin and salicylamide and contain an antihistamine (incidal).

Triominic Tablets and Syrup (A. Wander).—Each tablet contains phenylpropanolamine hydrochloride 50 mg., mepyramine maleate 25 mg., and pheniramine maleate 25 mg. 60 minims (3.6 ml.) of syrup contains 12.5, 6.25, and 6.25 mg. of the same compounds respectively. The drugs comprise two antihistaminics (mepyramine and pheniramine) and a vasoconstrictor decongestant (phenylpropanolamine).

There is no satisfactory evidence that antihistamines have any effect on the course of the common cold.

N.H.S. basic price: refagan, 10 tabs., 2s. 10d.; triominic, 50 tabs., 11s.; 2 fl. oz. syrup, 3s. 3d.

Correspondence

"Getting Married"

SIR,—I must protest most strongly against the recent publication by the B.M.A. of the book "Getting Married," edited by Dr. Winifred de Kok. I am appalled that those who authorized its publication were not aware of its possible damaging effect on the sex-conscious youth of our present day and age. This book, carrying as it does—and I think this is the vital point—the weight and authority of our Association, could well make even more difficult the task of parents seeking to instruct their children in accepted moral principles. I would mention that I am not a Catholic.

I am glad to learn from to-day's press that distribution of the book has been stopped, but I must tell you that, if it is resumed, I will in conscience be regretfully compelled to resign my membership of the Association.—I am, etc.,

London, W.1. GEORGE S. TURNER.

SIR,—May I be allowed to say how much I regret the publication of Dr. Eustace Chesser's article in the latest edition of the *Family Doctor* publication "Getting Married"?

I do not know what Dr. Chesser intended to convey in this hotch-potch of opinion and dogma, but I am sure that young people reading it will get the impression that "the doctors" believe that extramarital intercourse is not intrinsically wrong and that chastity is no more than a matter of individual preference. Without any argument I wish to go on record as one doctor who does not subscribe to this opinion.—I am, etc.,

London, N.3. G. W. PIPER.

SIR,—On Sunday, March 1, I was more than ordinarily displeased to see a full-page newspaper headline reading "Doctors in Free Love Storm: A Blow to Chastity." As this seemed to reflect no credit whatsoever on the fair name of our Association, and half suspecting that the matter had been grossly distorted, I read the booklet. Whilst much of it seems admirable, some I found noxious, and I was more than ordinarily disgusted that an article entitled "Is Chastity Outmoded? Outdated? Out?" should have been allowed to go out to the public in a booklet bearing on its cover the erstwhile proud distinction that it was "Published by the British Medical Association" as a sort of hallmark of authenticity and respectability. Regarding the article itself, although I read this several times I must say that I found the answer to the (? rhetorical) question given by Dr. Eustace Chesser to be about as useless and clear as a real thick smog; maybe this is because I too am more than ordinarily dense and archaic. What views, moral or otherwise, anyone expresses in his own name is his own business, but what goes out *in the name of the Association* is, I submit, the concern of every member. I think we might well ask ourselves but three questions: (1) Is the world at large and those about to marry (or not!) in particular likely to be the better for its counsel? (2) Could I as a doctor commend it to my patients? (3) Would I as a father wish my son to accept its standards? For myself I say No! No! No! I deeply regret that the booklet was issued by the B.M.A.

May I end by offering my whole-hearted support and congratulations to the Chairman of Council on his very prompt and courageous action in suspending circulation ?—I am, etc.,

Rugby. R. PRESTON HENDRY.

SIR,—It is a matter of grave importance when the leading professional organization in the country comes out with an attack on Christian morality. Surely the B.M.A. is, to say the least of it, unwise to make statements which cause scandal and pain to its Christian members and to others. Can a Christian continue to subscribe to an organization which puts out propaganda which he regards as sinful ?

The best course would be to repudiate these views, and withdraw the booklet.—I am, etc.,

London, N.W.4. R. W. COCKSHUT.

SIR,—Please add my protest to what, I have no doubt, has become a growing flood: I refer, of course, to the opening pages of "Getting Married," published by the British Medical Association—ungrammatical, inaccurate, and tendentious. To cite some examples:

Page 38: "If left alone, we would [? should] perish," as would baby rats. Page 40: "[A relationship] which presupposes the acceptance of each as they really are." . . . "Since each, unbeknown to the other, would be using his partner merely for their own personal satisfaction." Page 41: "Freed of [? from] preconceived ideas and prejudices."

Page 38: "One woman in every three at the present time in this country admits to [*sic*] premarital intercourse." This is patently untrue: perhaps the author means, Of those questioned by me one wife in three admits (or confesses *to*) premarital intercourse. "One in eight births would have been illegitimate but for the subsequent marriage of the parents." Page 54: "One bride in eight is already having a baby at the time of her wedding." These statements cannot possibly both be true.

Page 40: "[The double standard of morality] has up till now been based on the functional differences between the sexes. . . . But with the advent of female emancipation, with all that is implied, the functional differences have lost much of their meaning." So has this sentence—unless it means that men now conceive and bear children. Page 41: "And a shocking price has [*sic*], and is, being paid for by [society's] unforgivable hypocrisy." Delete "by" and some trace of meaning can be extracted from words which as they stand have none.

Pages 40 and 41: "By the kind permission of society, we are allowed to lose our chastity when married. All too often events prove this to be too little and too late." For as far back as human records go, a wife's chastity throughout her married life has been reckoned her brightest jewel. And I firmly believe that the great majority of all the millions of married people in this country live in entire chastity during the whole of their married lives, and would be revolted to think anything else possible. As for the second sentence, anyone who can extract an intelligible meaning from it deserves a D.Litt.

No wonder the popular press is smacking its lips. It will take long to assess the harm this publication has done the Association in the eyes of the general public; and recovery will take longer still.—I am, etc.,

Cambridge. E. WATSON-WILLIAMS.

SIR,—I wish to register a very definite protest at the publication under the aegis of the British Medical Association of such a booklet as "Getting Married." Words cannot express my sense of shock and disgust at some of the expressions of opinion contained therein, which are the antithesis of all that is truly Christian.

I have cancelled my order to my bookseller for *Family Doctor*, as this appears in my waiting-room and I would hate my patients to think that I associate myself with teaching of this sort.—I am, etc.,

Shaftesbury, Dorset. R. W. PINNIGER.

SIR,—I am appalled that a book published by the British Medical Association in good faith, and setting out the views of the contributors on matters of immediate social importance, should be withdrawn in response to the pressure of special groups, and without any reference to the members of the Association. I refer, of course, to "Getting Married."

The profession is not an arbiter of private morality. Dr. Solomon Wand should be waved again. If the attitude of the Association's Council supports this prejudiced and timorous action, I am sure I shall not be alone in withdrawing from the Association.—I am, etc.,

London, W.1. B. S. COOPER.

Obstetric Problems in G.P.

SIR,—Mr. S. Bender (*Journal*, February 21, p. 497) advises intravenous ergometrine at the end of the second stage of a domiciliary forceps delivery under local analgesia, but he considers that the presence of a second doctor is necessary. An alternative, based on the principle of doing nothing that can be done by the midwife, is to deliver the head, remove the forceps, hand over delivery of the shoulders to her, and give the intravenous injection oneself. There is plenty of time, particularly if the patient is keeping herself in relative oblivion with trichlorethylene.

When only two persons, doctor and midwife, are present, it is especially important to avoid simultaneous post-partum haemorrhage and foetal apnoea. A combination of local analgesia and second stage intravenous ergometrine virtually abolishes the former and reduces the chances of the latter. To give the ergometrine is well worth while, and the only price to be paid is the need for a second pair of gloves for repair of the perineum.—I am, etc.,

Hucclecote, Gloucester. IVOR COOKSON.

Serum Gonadotrophin in Acne

SIR,—I disagree with the conclusions drawn by Dr John H. S. Pettit (*Journal*, February 28, p. 557). I am still having good results with tablets of serum gonadotrophin in patients with acne vulgaris. A mild exacerbation between the third and sixth weeks is not uncommon, and improvement cannot be judged until after ten weeks. Many of my patients receive no other treatment. These tablets are soluble in saliva and are inactivated by the stomach. Absorption from the mouth is therefore essential, but dissolving the tablets in the mouth and absorption through its mucous membrane are two different things. Most of my failures have been due either to dissolving the tablets under the tongue instead of putting them between the gum and the cheek or to sucking them vigorously. In both cases the gonadotrophin is, in fact, dissolved in the saliva and swallowed. The tablets should take between three-quarters of an hour and two hours to disappear. When they go more quickly improvement cannot be expected. Perhaps these points explain Dr. Pettit's results.—I am, etc.,

London, W.1. E. LIPMAN COHEN.

Mental Health Bill

SIR,—"Psychopathic disorder": this term, which traditionally is a source of argument in psychiatry, has, by the provision of the Mental Health Bill, been extended into the psychiatry of childhood. It will be applicable from infancy onward, and a child may be admitted or detained in a mental hospital on the basis of psychopathic disorder. This is defined in Part I, Clause 4 (4).

Psychopathic disorder is a term largely inapplicable to children and adolescents. Clinically the term psychopathic implies a mental state characterized by immaturity of emotional attitudes, values, and behaviour —i.e., qualities characteristic of childhood and adolescence. Children and adolescents may show reactively "abnormally aggressive behaviour or seriously irresponsible conduct" over a period of time, without the implication conveyed by psychopathic disorder in adult life. More briefly, a psychopathic adult is one who behaves as does a child or adolescent under stress.

It is in principle highly undesirable that the term with all its implications should become current as applied to children. Used as in the Bill, it allows of a wide group of children and adolescents being subject to admission to hospital by application who would never have been subject to certification. As there is nothing in the Bill that denies parental authority either held by the parent or vested in some other party in children up to the age of 16, it would seem sufficient that admission or retention of a child up to the age of 16 should be on the authority of the parents.—I am, etc.,

Edenbridge, Kent. KENNETH CAMERON.

SIR,—When this Bill becomes Act there may still remain an important defect in the Mental Health Service which will make it less attractive than it should be to medical men, the majority of whom are staunch individualists. I refer to the extensive authority of the medical superintendent over every other member of the hospital medical team, consultants and S.H.M.O.s included.

Psychiatry has lost much, on the one hand, by the diversion of its most able men to non-clinical work, on the other hand by the obstructions to creative thinking implicit in the quasi-military atmosphere of some mental hospitals. It would be to the great advantage of the Service if its medical and administrative structures were remodelled to approximate as closely as possible to those of general hospitals. This could readily be accomplished by the repeal of Statutory Instrument No. 419, National Health Service Regulations, 1948 (Superintendents of Mental Hospitals, etc.), dated February 26, 1948. The executive functions of medical superintendents could be efficiently discharged by lay administrators who are trained specifically for such work. Medical advisory duties would devolve upon the medical advisory (or staff) committees, which should now be functioning smoothly and efficiently as laid down in Ministry of Health Memorandum No. 94101/2/77, dated August 15, 1953 (Leaflet H.M.C. (53)87).

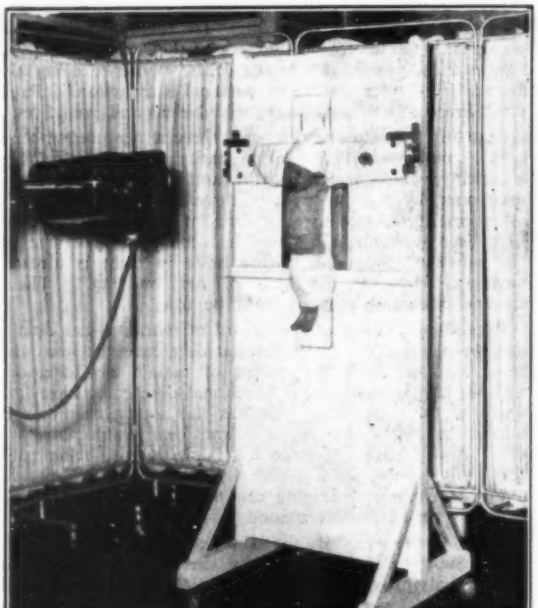
In Part IV, Clause 58, of the Mental Health Bill (and in similar interpretations in other parts) the meaning of "the responsible medical officer" requires reconsideration, otherwise even consultants may find themselves merely assistants, as were their predecessors before 1948. A litigious patient might, for example (assuming for the sake of argument that the above-named Statutory Instrument is not repealed), claim, in order to obtain discharge, that the renewal of his detention under Clause 43, paragraph 3 (a), was illegal, by reason of the fact that the medical superintendent was the medical practitioner in charge of his treatment, and that the consultant or S.H.M.O. who made the examination and report was, in law, an assistant, and therefore not "in charge of" treatment. Clause 58(1) (lines 14 and 15 of page 39 of the Bill) should be amended to read "the medical practitioner who has clinical responsibility for the treatment of the patient"; "clinical responsibility for" is the phrase used in our Form of Contract and would therefore pin-point the consultant or S.H.M.O. concerned. It is a more precise term medically than "in charge of."

—I am, etc.,

St. Lawrence's Hospital, Bodmin. J. B. DEDMAN.

Protective Screen for Neonatal Radiography

SIR,—Over four-fifths of the infants admitted for operation to the Neonatal Surgical Unit at Alder Hey Children's Hospital suffer from obstruction of the alimentary tract. Radiological examination is essential for diagnosis, and experience has shown that one straight antero-posterior picture is all that is required for diagnosis in the majority of cases. Exposure of the infants to radiation is thus kept at a minimum. But a nurse holding several of these infants during radiography is subjected to a considerable exposure to



radiation in the course of time. The wearing of protective lead aprons and lead gloves is not adequate protection. An apparatus for holding the cassette recently described by Willis Potts in his Moynihan Lecture[1] does not protect the nurses from radiation.

The protective screen illustrated has been found quite useful. The screen is 5 ft. 6 in. (1.6 m.) high and 2 ft. (0.6 m.) wide, and contains lead sheeting between two layers of plywood. It stands on castors and is easily movable. The infant is bandaged on a plywood crucifix as shown. The head tends to fall forwards and should therefore also be bandaged to the crucifix. A rack allows suspension of the crucifix at different levels in front of the radiographic plate. The plate is placed behind the crucifix between two wooden rails.

This screen as well as the *x*-ray machine are kept in the neonatal surgical unit, so the infants are not exposed

to infection by sending them to the Radiological Department. If any manipulations are necessary during radiography—for instance, the passing of a radio-opaque tube in order to diagnose oesophageal atresia—the attending nurse can stand behind the lead screen. In general it is not necessary for a nurse to stand near the child when a picture is taken.

The screen was built for us by Messrs. Green, E. Roberts, & Sons, 49a, Hardman Street, Liverpool.

—I am, etc.,

Alder Hey Children's Hospital, Liverpool, 12. P. P. RICKHAM.

REFERENCE

[1] Potts, W. J., *Ann. roy. Coll. Surg. Engl.*, 1958, **23**, 275.

Auto-immune Erythrocyte Sensitization

SIR,—We found Dr. J. Darnborough's paper on "A Unique Case of Auto-immune Erythrocyte Sensitization" (*Journal*, December 13, p. 1451) particularly interesting, as for more than a decade the role of auto-antibodies and what we have called the hyperreactive auto-allergic state in the pathogenesis of disease has been under investigation at this Institute. In the course of these studies the direct Coombs test for sensitization of red cells was carried out on the blood of patients with a variety of these conditions, as well as on the blood of patients suffering from other diseases, and on the blood of normal controls.

It was found that this test gave positive results in a proportion of cases of acute disseminated lupus erythematosus, dermatomyositis, periarteritis nodosa, rheumatic fever, and some other conditions, as well as in cases of acquired haemolytic anaemia. The blood from some patients with infections including tuberculosis, malaria, and trypanosomiasis was also found to give positive results, but in most instances were negative, as were the normal controls.[1-4]

We suggest, therefore, that the positive result given in the direct Coombs test by Mr. X's blood does not necessarily indicate an active auto-immune haemolytic anaemia, as in fact there was no clinical or haematological evidence of this. It thus seems possible that it is an indication of an infection acquired during the past two years, or of a collagen disease, or another of the auto-allergic conditions.

As Mr. X is a coalminer a chest *x*-ray examination may be of value, as there is some evidence that in some degree the reactions in silicosis and other pneumoconiosis may have an immunological basis. As Mr. X was a blood donor, a positive Wassermann reaction has doubtless been excluded. In our study it was found that a large proportion of bloods giving a positive Wassermann or Kolmer reaction also gave a positive result in the direct Coombs test. This has been found in newborn infants of mothers with positive serological reactions as well as in adults. Desirable additional information at this stage would be the results of the analysis of the serum proteins and of the tests for L.E. cells.

Dr. Darnborough will be making a valuable contribution if he can keep Mr. X under observation for a few years, and then present a report on developments.—We are, etc.,

A. ZOUTENDYK.
JAMES GEAR.
The South African Institute for Medical Research, Johannesburg.

REFERENCES

[1] Zoutendyk, A., and Gear, J., *S. Afr. med. J.*, 1951, **25**, 665.
[2] Marshall, J., Zoutendyk, A., and Gear, J., ibid., 1951, **25**, 764.
[3] Gear, J., *Acta med. scand.*, 1955, **152**, Suppl. 306, 39.
[4] Zoudendyk, A., and Gear, J. H. S., *Brit. med. J.*, 1950, **2**, 1175.

Reappraisal of Thymectomy

SIR,—I read with great interest your leading article on the reappraisal of thymectomy (*Journal*, January 31, p. 288). This April there will be an international conference on myasthenia gravis sponsored by the Myasthenia Gravis Foundation of New York, at which a British delegation will participate, and no doubt the subject of thymectomy will be once more on the agenda.

Sir Geoffrey Keynes states in his paper on thymectomy[1] that myasthenia gravis is a disease that never obeys any rules. He must have been puzzled with many problems, because in a subsequent paper[2] on this subject he had to title it "second and third thoughts." Until recently the thinking about the natural history of this disease or syndrome has been rather uncertain, with the result that the statistical analyses of thymectomies at the various surgical centres were conflicting. In a recent report[3] of 282 cases of myasthenia gravis seen at the Mount Sinai Hospital, New York, we were able to suggest a clinical classification whereby the effects of medical treatment and prognosis can be more clearly foreseen. In my experience the application of edrophonium chloride by Dr. Osserman and Dr. Kaplan[4] as a means of differentiating between a myasthenic and cholinergic state during drug therapy with anticholinesterases has been a great advance in the medical management of these cases. Our increasing skill in the application of a tracheotomy and the respirator has reduced the mortality due to respiratory paralysis. At a recent meeting of the Royal Society of Medicine Mr. J. E. Piercy[5] stated that tracheotomy had become invaluable in the management of a myasthenic or cholinergic crisis.

If we compare Simpson's analysis[6] of thymectomies performed by Sir Geoffrey Keynes and the current analysis of the medically treated cases at the Mount Sinai Hospital[7] (see Table), the figures show that a fourth thought about thymectomy may be necessary.

	Results of Surgical Treatment[6]		Results of Medical Treatment[7]	
Result	Females 182	Males 76	Females 212	Males 113
A. Remission	22%	19·1%	15%	
B. Considerable improvement	13·2%	10·5%	30%	
C. Moderate "	23·1%	23·7%	17%	
D. Same or worse	17·6%	19·7%	D., E., F. 20%	
Deaths	17%	21%	18%	

Simpson's classification D. can be compared with D.+E.+F. of Osserman. All tumour cases are excluded.

—I am, etc.,

London, W.1. H. WINDSLEY.

REFERENCES

[1] Keynes, G. L., *Brit. med. J.*, 1949, **2**, 611.
[2] —— *Lancet*, 1954, **1**, 1197.
[3] Osserman, K. E., *et al.*, *Arch. intern. Med.*, 1958, **102**, 72.
[4] —— and Kaplan, L. I., *Arch. Neurol. Psychiat. (Chicago)*, 1953, **70**, 385.
[5] Piercy, J. E., 1959, personal communication.
[6] Simpson, J. A., *Brain*, 1958, **81**, 117.
[7] Osserman, K. E., *Myasthenia Gravis*, 1958, p. 211. Grune and Stratton, New York.

Immunization Programmes

SIR,—Immunization programmes at the present time must compromise between theoretical and practical desiderata. Our programme in this city is: triple antigen at 2, 3, and 4 months; smallpox vaccination at 5 months; poliomyelitis immunization at 6, 7, and 14

months; booster "triple" at 18 months and 5 years. We advise the mothers about this within a month of the baby's birth. Many of the family doctors follow this scheme.

Large-scale immunization, which is essential, is only successful if well organized on a definite plan. This applies to the work of family doctors just as well as to the work of local health authorities. In my view, therefore, some degree of stability in the programme in any area is desirable and chopping and changing should be avoided unless very clearly necessary.

Although I have been advocating whooping-cough vaccination from 2 months of age since 1952, and have recommended combined whooping-cough–diphtheria vaccination at 2 months of age since 1954, and triple antigen from 2 months since 1957, even now (quoting 1958 figures) only two in five of the babies have completed a full course of triple or double antigen before 7 months of age, and only about one in six have done so by 5 months of age.

Accurate notification is the only basis for sound evaluation of immunization programmes, but tetanus is not notifiable and whooping-cough is probably very much under-notified. Diphtheria is now rare, but few of us can doubt the value of immunization against these various diseases. Although I well recollect the severe diphtheria of a generation ago, whooping-cough seems to me at present to be the main foe against which early immunization is essential.

The following jingle by Dr. James Kelman[1] (M.O.H., Perthshire) is an amusing reflection on immunization procedures. But the bairns of to-day might think those of three years ago were lucky.

"I was only born six months ago,
But I wish I hadnae come:
It's been naething but injections
Since I parted from ma mum.
Afore I'd time tae draw ma breath
I'd a dose of B.C.G.,
And when I wasnae lookin'
They vaccinated me.
Since then it's been diphtheria
Along wi' whoopin' cough.
By golly, there's nae doot ava'
We bairnies sure are tough."

—I am, etc.,

Health Department, Exeter. E. D. IRVINE.

REFERENCE

[1] Kelman, J., *Municipal Engineering*, 1954, **131**, 985.

SIR,—Dr. John B. Longmore (*Journal*, February 21, p. 505) agrees with the medical officers of health of certain metropolitan boroughs (*Journal*, February 7, p. 362) that B.C.G. vaccination be given at the age of 13. I would suggest that more use should be made of the neonatal period for B.C.G. vaccination, as it is a more appropriate time prophylactically and administratively. If the vaccination is done within days of birth our pin-cushion baby is spared the pre-vaccination tuberculin test and the mother has time to discuss the procedure with the hospital staff. It is extraordinary how little the average parent knows about tuberculin testing and B.C.G. vaccination.

In support of neonatal B.C.G. vaccination I might add that in this village of less than 3,000 six pre-teenage children with active primary tuberculosis have been discovered in the past two months. During the same period the 1-year-old brother of one of these children died from bronchopneumonia, presumably tuberculous, while only one person over 12 years developed primary tuberculosis. By making B.C.G. available at *all* maternity units I believe that many young children can be spared the upset of a spell in a sanatorium or worse, and the mothers can be given an idea of what is being done to their children.—I am, etc.,

Pontlottyn, Glamorgan. P. P. ROWAN.

Noradrenaline-secreting Neuroblastomata

SIR,—Since the report from this department[1] of an adrenaline-secreting neuroblastoma we have been awaiting opportunities of studying the secretory functions of these tumours. In view of the article by Drs. H. Isaacs, M. Medalie, and W. N. Politzer on noradrenaline-secreting neuroblastomata (*Journal*, February 14, p. 401) we would like to record the following case.

A child aged 20 months was admitted to hospital with a large abdominal tumour in the left renal area, unilateral proptosis, and marked anaemia. Radiological examination confirmed the presence of multiple secondary deposits in the mandible, pelvis, and femur, together with speckled calcification in the tumour. Hb was 8.7 g./100 ml. and W.B.C. count 11,380/c.mm., with no abnormal cells. At laparotomy a large tumour was found at the site of the left adrenal gland extending across the midline. Removal being impossible, a large section was taken for biopsy and assay of pressor amines. The child was given palliative local radiotherapy and massive vitamin-B_{12} therapy, but died at home two months later. The blood pressure of the child taken 24 hours after the operation was 110/70.

Histological examination of the tumour showed the appearances of a neuroblastoma throughout the section and no adrenal tissue could be found. Assay of an extract of part of the tumour showed it to contain 5.5 μg. of pressor amines per g. of tissue (wet weight), 26.9% as adrenaline and 73.1% as noradrenaline. Post-operatively the urine was examined and a single specimen found to contain 0.17 μg. of free pressor amines per ml.

We would like to endorse the final opinions of the authors of the above articles and suggest that routinely urinary pressor amines should be estimated in children with neuroblastomata, and whenever possible the tumour itself should be assayed for pressor amines.—We are, etc.,

N. A. WYNNE.
D. WHITEHOUSE.

Department of Child Health, King's College, University of Durham.

REFERENCE

[1] Mason, G. A., Hart-Mercer, J., Millar, E. J., Strang, L. B., and Wynne, N. A., *Lancet*, 1957, **2**, 322.

Future of the Tuberculosis Service

SIR,—Dr. L. E. Houghton, in his letter in the *Journal* of February 28 (p. 583), pleads that open-air hospitals should be retained and considers that patients with pulmonary tuberculosis and renal tuberculosis should continue to be treated in them. I would like to support Dr. Houghton and to take the opportunity of re-emphasizing the need of open-air therapy, for such it is, in the treatment of skeletal tuberculosis. This was well recognized by the original generation of orthopaedic surgeons. To quote from Girdlestone's book,[1] "It is this part of the treatment that can only be carried out in open-air country hospitals, and it was in 1910 that the author first came across such a hospital in Shropshire. During his time in the wards of a London hospital, first as a student, then as a house-surgeon, Pott's disease and hip disease had meant deformity, septic complication, and the slow, miserable process of lardaceous disease. In contrast to this the

work of Sir Robert Jones in open-air hospitals in Shropshire and at Heswall seemed miraculous." These are strong words, but they do not exaggerate, as I and many others can testify from similar experience. There is danger now that this valuable therapeutic method may be lost, as it may be supposed that antibiotic treatment can take its place. Experience has shown that the results of the treatment of skeletal tuberculosis by rest and antibiotics alone are inadequate compared with those obtainable when open-air therapy is also available.

I would also like to support Dr. Houghton in his plea that there are other conditions which might be expected to do well in an open-air hospital and would like to add to those he mentioned rheumatoid arthritis. A unit for the long-term treatment of certain forms of rheumatoid arthritis has been in being at this hospital for four years and the results of this method of treatment are at present under scrutiny and are to be reported. On the general aspect of the use of these hospitals, it should be remembered that they have in the past been brought to a high standard of medical and surgical efficiency, that urban civilization is now producing stress diseases, and that some degree of rural tranquillity may well serve as an antidote. Difficulty of visiting is often raised as an objection, but this can be largely met by the organization of special bus services and visiting hours suited to the needs of visitors from a distance. Medical and surgical staff should also be available from the urban centres to visit them.—I am, etc.,

M. C. WILKINSON.

Black Notley Hospital, Essex.

REFERENCE

[1] Girdlestone, G. R., *Tuberculosis of Bone and Joint*, 1940. Oxford University Press, London.

Antibiotics in Acute Tonsillitis and Otitis Media

SIR,—I found Dr. Peter Walford's letter on antibiotics in acute tonsillitis and otitis media (*Journal*, February 7, p. 368) in its inferences utterly at variance with my experience. I have not enough knowledge to argue on the question of penicillin with the object of preventing rheumatic fever or nephritis, but I should be sorry if anyone inferred from his letter that penicillin was not a suitable treatment for certain streptococcal throats. To the child with massive glands and sloughs on the tonsils it is a godsend, as it is to many other cases with severe toxaemia.

It is really in the case of acute otitis media that I take issue with him. Knowing the great anxiety and occasional poor results of the treatment of acute otitis media in pre-antibiotic days, and the relative ease of treating it nowadays, I feel that the right treatment for all acute otitis media is penicillin in the first instance. By that I mean, in severe cases, intramuscular penicillin, one mega unit daily for five days; and in the less severe cases one mega unit initially, followed by oral penicillin V for five days.

In the old days, I have done as many as nine myringotomies in one day. I did one to-day for the first time for many months. The object of treatment, as I see it, should be to restore the glistening, intact drum with normal detail and hearing. How does one know which are the 75% of cases equally well treated without antibiotics?—I am, etc.,

F. B. P. EVANS.

Tewkesbury, Gloucestershire.

SIR,—I am pleased to see Dr. Peter A. Walford's (*Journal*, February 7, p. 368) critical attitude to this problem, as the treatment of those illnesses that commonly affect our patients should particularly be under continual review. However, I most strongly disagree with his suggestion that the case of acute otitis media which is already discharging is more in need of antibiotics than the one that is not. I should have thought the opposite the case, since drainage aids resolution. It is the one without discharge that can be so dangerous, as there is then often nothing gross to draw attention to the fact that infection persists. Because the drum does not perforate in a case of otitis media does not mean that the infection is a mild one. Only last week I operated on a child for Mr. Stephen Young. She had had occasional earaches for the past two months but never otorrhoea. She had a red intact drum, fluctuant post-aural swelling, pus coming through a hole in her mastoid cortex, and a perisinus abscess present at operation.

With regard to my paper[1] to which Dr. Walford refers, of course the selection of those children whose mothers chose to bring them along for follow-up four years after treatment, in response to my circular, depended on the mothers themselves and probably many other chance factors. I was at pains to point out that the series was far from ideal. However, the final hearing result must be the yardstick by which we judge any treatment, and yet the fact remains that, complete or incomplete, there are very very few papers giving audiometric results to support a particular line of treatment. My review was, I maintain, an attempt in the right direction, and the results were in accord with the clinical experience of the E.N.T. department at the Radcliffe Infirmary, Oxford, that the method of treatment (regular penicillin injections without a myringotomy) was sound.

Perhaps the virulence of these infections has so diminished that now careful observation without any antibiotic initially is reasonable treatment, especially for the mild case, and that penicillin by injection is over-treating a condition that frequently settles by itself anyway. Let us hope so, if only to avoid frightening injections. I am well aware that only a few, selected, more severe cases are seen by hospital staff. Careful observation without any antibiotic initially is certainly safer than inadequate antibiotics and inadequate observation to detect persisting infection.

Whatever we do we must obtain audiometric records to support it with preferably a much better percentage follow-up than mine could be.—I am, etc.,

J. W. DIXON.

Glasgow.

REFERENCE

[1] Dixon, J. W., *J. Laryng.*, 1958, **72**, 227.

Dirty Food

SIR,—British people have little right to complain when they are called dirty feeders, or more politely eaters of dirty food. They need food inspectors with wider powers and responsibilities than at present to protect them.

Almost anywhere that food is served we find sugar, butter, jam, and other edibles exposed to flies and dust. Water is rarely freshly drawn just before meals. Cups and glasses too often handled by fingers inside, spoons and forks by their bowls or prongs. It is uncommon to see any attempt to destroy and sweep up flies. The best establishments are not blameless, but we recognize the difficulty of finding and training suitable employees. There is not much covered glass and crockery available, and makers would say no doubt that there is little demand. There would be more washing-up, more breakages, and expense.

It would not be easy to remedy all these failings, but if we could not come near to perfection we ought to

approach it. Lectures on hygiene for senior classes in the schools would be helpful, but quicker results might follow pressure on the Ministry concerned to make new regulations and enforce them. Such pressure would come most effectively from the B.M.A.—I am, etc.,

Malvern. W. A. BOWDLER.

Children's Footwear

SIR,—Certain of our national newspapers have recently taken an interest in children's footwear. Sir John Charles's current report[1] mentions the high proportion of school-children found to have badly fitting shoes, and *The Times* (January 12, p. 11) has noted the short period of useful wear obtained from children's shoes and the difficulties involved in buying a pair that fit.

Is it any wonder, then, that in this poor area I cannot recall in the last three years seeing a single child over 3 years old with 10 *straight* toes, entirely devoid of blisters, corns, or callouses ?—I am, etc.,

Manchester Child Welfare Centres, Manchester, 14. DAPHNE SASIENI.

REFERENCE

[1] *Report of the Chief Medical Officer of the Ministry of Education for the Years 1956 and 1957*, 1958. H.M.S.O., London.

Optic Neuropathy after Antimony

SIR,—I was interested to read Dr. D. M. Forsyth's article on "Visual Disturbances Associated with Trivalent Antimony Salts" (*Journal*, November 22, p. 1272). If the procedure outlined in the article is the routine method of treatment adopted at Kuwait, it is evident that repeated courses of antimony are given at relatively short intervals, and one would expect the patients to have shown severe preliminary reactions to antimony in the form of cough, muscle pains, itching, vomiting, etc., before reaching the stage of visual disturbances reported.

Antimony is a heavy metal with a cumulative action, and it is of little value to re-examine the urine immediately after treatment. It is our practice here to re-examine specimens for ova two months after the completion of a course of treatment, whether with the highly potent intravenous sodium antimony tartrate, the less potent intramuscular lithium antimony thiomalate, or the least potent oral lucanthone hydrochloride. Sometimes we are urged by the traditional anxiety of our Egyptian and Sudanese patients (who are of almost identical psychological make-up to the Kuwaitians) to take specimens earlier, immediately the course of treatment has ended, and sometimes before that, but usually that anxiety can be overcome by reassurance. Nevertheless, it is difficult in endemic areas to differentiate, from the mere presence of ova in early or late specimens, between a reinfection and exacerbation of a dormant one. In my opinion, however, it is best to rely on the cumulative action of the antimony and to give the patient the benefit of lapse of time; late specimens should be taken before embarking on further courses of treatment.—I am, etc.,

Kosti, Sudan. F. SHAMS EDDIN.

Trypanosoma rhodesiense in Bushbuck

SIR,—Dr. M. T. Ashcroft's letter (*Journal*, January 17, p. 173) drew my attention to the paper by Fairbairn and Burtt,[1] of which I have now, by the courtesy of a colleague, seen the original publication. Referring to this paper Dr. Ashcroft writes: "The evidence suggests that the polymorphic trypanosomes are morphologically identical and differ in physiological properties only; one of these, the infectivity to man, is, as pointed out above, stable and separates *T. rhodesiense* and *T. gambiense* from *T. brucei*, but others, such as virulence, are variable and influenced by the mammalian host of the trypanosome." I regard virulence, host-proclivity, and transmissibility as all potential variables in the struggle for survival of a parasitic protozoon. In Uganda we obtained plenty of evidence of the host's influence on the attributes of a strain; as, for example, in two series of experiments in each of which a man and either one or two laboratory animals were inoculated, *by the syringe* on the same day, with blood carrying a strain of *T. rhodesiense* that had been passaged directly through a series of 13 guinea-pigs; all the animals and neither of the men became infected.

I agree with the authors that individual volunteers differ in their resistance; but so also, I believe, do strains of mammalian trypanosomes. Here are some examples. *T. congolense* and *T. nanum* are both primarily parasites of ruminants, but the former is able also to infect laboratory animals. The two are morphologically identical, the former usually more virulent, and are distinguished only by their range of hosts. Years ago, Yorke and his colleagues persuaded *T. nanum* to infect species of animals hitherto held to be immune to it. More recently, in Uganda, a strain of *T. congolense*, maintained for many months in monkeys, showed definite signs of losing its ability to infect this species, though still developing fully in tsetse.[2] *T. vivax* has also been induced to infect animals outside its orthodox range of hosts, but in doing so was found to have lost its power to develop in tsetse.[3] Hoare,[4] has described how certain laboratory strains of *T. brucei* became monomorphic, and so indistinguishable from *T. evansi*; and, vice versa, *T. evansi* became polymorphic, with posterior-nuclear forms. There are also the otherwise inexplicable instances of the infection of laboratory workers in Europe with species of trypanosomes supposedly non-pathogenic to man.

I do not accept the authors' conclusion that all the failures in Uganda to infect man are simply explained by the salivary gland inoculum not containing enough trypanosomes. A striking feature of these failures was the regularity with which the same flies, when fed on animals 48 hours before or after biting man, invariably infected them. The great majority of our gland-infected flies had heavy gland infections, and all flies were starved for at least 48 and often 72 hours before feeding on man, and human blood was found in the gut on final dissection. In only one strain of *T. rhodesiense* was there anything unusual in the gland infections. For, in striking contrast to all the other strains studied at Entebbe, the gland infections, during over three years' maintenance at the laboratory in antelope and other animals, always showed only very few trypanosomes. Five different men were fed upon respectively by 8, 9, 6, 5, and 4 gland-infected flies carrying this strain, and none were infected; but monkeys and other animals bitten by the same flies all became infected. If this strain had been isolated originally from a wild antelope instead of from a native woman, how would it have been classified ?

The authors' experiments with probe-test feeds on to a slide led them to conclude that 300–450 salivary gland

forms was about the minimum dose necessary to infect the average man with their strain of *T. rhodesiense*. But they also showed that men inoculated with 680, 800, and 1,067 gland-forms failed to become infected; also that a single fly which ejected very few trypanosomes infected one out of three men. Differences in man's resistance must play an important part in the survival of a trypanosome in areas where he is seriously encroaching into game country, driving out the game, and so becoming of increasing importance to the parasite's intermediate host, the tsetse.

In conclusion I believe that the soundest course is that suggested by Hoare[6]—namely, to regard *T. brucei*, *T. gambiense*, and *T. rhodesiense* as biological races of a polymorphic species, one of whose potential hosts is man, their distinguishing features being determined by the environment in which they exist in nature.—I am, etc.,

Cross-in-Hand, Sussex. H. L. DUKE.

REFERENCES

1 Fairbairn, H., and Burt, E., *Ann. trop. Med. Parasit.*, 1946, **40**, 270.
2 Duke, H. L., *Proc. roy. Soc. B*, 1912, **85**, 554.
3 Nash, T. A. M., *A.R. W. Afr. Inst. Trypanosom.*, 1955, p. 16.
4 Hoare, C. A., *Ann. Soc. belge Méd. trop.*, 1947, **27**, Suppl. 267.
5 —— *Biol. Rev.*, 1943, **18**, 137.

Hula-hoop Syndrome

SIR,—Mr. F. R. Brown (*Journal*, February 7, p. 369) asks why human beings, dogs, snails, and runner beans prefer to behave or to grow in a right-handed (or a left-handed) way. Some such tendency is, as he says, an almost universal property of living things.

We can begin the explanation at almost any level. Gilbert and Sullivan started at the political level, but perhaps the chromosome and the genes are the most relevant to the biological aspect of the problem. These are now regarded as coiled structures, and presumably, if they were coiled the other way, the whole subsequent development would be reversed in direction. But an essential part of the coiling is the right or left handedness of the basic molecules from which they are built and which, in turn, determine the selection or synthesis of other asymmetric molecules which go to build up the organism. Thus, if we could enter the fourth dimension and return the "other way round"—like a two-dimensional lantern-slide being turned in the third dimension and inserted into the projector the wrong way round—all natural foods would become unavailable or poisonous and we should need to eat foods composed of the synthetic mirror-images of natural molecules.

Perhaps the "handedness" of all subsequent life was determined the first time an asymmetric molecule was incorporated into an early organism. We might regard this as due to chance and suppose that, if life on many thousands of planets could be examined, we should as often find the basis of life to be one set of compounds as their opposites. But now we cannot be sure even of this, for while, until a few years ago, physicists regarded the laws of Nature as indifferent to right and left, they now have had to admit the "failure of parity" and to see the whole universe from the ultimate particle to political and intellectual man as riddled with a tendency to the right or the left—or should I say the left or the right?—I am, etc.,

Blood Group Reference Laboratory, The Lister Institute, London, S.W.1. A. E. MOURANT.

SIR,—Mr. F. R. Brown's letter (*Journal*, February 7, p. 369) prompts me—not only as a grateful student and one-time acolyte of his, but also as one who has travelled the globe fairly widely—to contribute my thoughts to his query.

It is easy to confirm that the whirlpool formed when a bath plug is pulled out revolves in a clockwise direction of progress of the water. This conforms with Mr. Brown's personal observation that the runner bean and snail-shell whorl clockwise in the direction of their growth.

Seafarers will say that the bath water will whorl in the opposite direction on the other side of the equator. Although I have crossed the line five times during my life I have never made personal observation of the accuracy of this lore. Presumably on the geodetic equator there should be no whirlpool at all. It would be fascinating to hear whether the beans and snails of Capricorn are opposed to those of Cancer.

If truth be in these beliefs, maybe the explanation for the preponderance of "right-handedness" lies in the superimposition of a central nervous system upon an obscure natural geodynamic trait.

I suggest this can be explained anatomically by the easier access of blood to the left cerebral hemisphere by way of the left internal carotid artery as compared with that of the right. Incidentally I regard this slightly delayed arterial pulse on the right side as the most likely reason for there being no blood stasis at points in the circle of Willis.—I am, etc.,

Gobowen, Salop. R. P. W. KUP.

Reynolds's Two Heads of John Hunter

SIR,—I see in Mr. W. R. LeFanu's article (*Journal*, February 28, p. 580) that he refers to the face of John Hunter "thinned and distorted by illness, with the eyes slightly convergent." It looks to me from the picture as though the eyes are definitely divergent.—I am, etc.,

London, W.1. T. KEITH LYLE.

Flats for Retired Doctors

SIR,—I should be grateful if you would afford me the hospitality of your columns to bring to the notice of the medical profession a new venture of the Royal Medical Benevolent Fund. Owing to the generosity of the late Mr. J. T. M. Giffen, F.R.C.S., a house has been purchased in an attractive residential area off Putney Hill. It has been converted into five self-contained flats and has a large and pleasant garden. Each flat consists of sitting-room, bedroom, kitchen, bathroom, and lavatory, and the rooms are by no means small.

These flats are rent-free and are intended for retired doctors and their wives in reduced circumstances. A maintenance charge of £25 per annum is to be made and residents will supply their own heating and lighting. The conversion of the house into flats is almost complete.

The Committee will now be glad to receive inquiries from any members of the medical profession who might consider applying for one of these flats. Fuller information will be given by the Secretary, Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, London, S.W.15, to whom all communications should be addressed.—I am, etc.,

R. M. HANDFIELD-JONES,
Chairman, Committee of Management, Royal Medical Benevolent Fund.

Obituary

Sir PERCIVAL NICHOLLS, K.C.B., F.R.C.S.

Surgeon Vice-Admiral Sir Percival Nicholls, a former Medical Director-General of the Navy, died at Haslar on March 1 at the age of 81.

Percival Thomas Nicholls was born on May 8, 1877, the son of Harry and Ellen Nicholls. He studied medicine at the Middlesex Hospital, and after qualifying in 1900 he held the posts of house-physician at the Middlesex Hospital and house-surgeon at the Brighton and Hove Hospital. He entered the Royal Navy as surgeon in 1901, and served for short periods in a number of ships and establishments. He was promoted to the rank of staff surgeon in 1909. In 1907 he was awarded the Order of the Crown of Italy for services rendered at the time of the Messina earthquake. Serving throughout the first world war, he became fleet surgeon in 1915. He was promoted surgeon captain in 1926, and a year later he became principal medical officer at the Royal Naval Barracks, Portsmouth. In 1929 he became senior medical officer of the Medical Section at the Royal Naval Hospital, Haslar, an appointment which he held for three years. He was promoted surgeon rear-admiral in 1932 and appointed medical officer-in-charge of the Royal Naval Hospital, Malta. Admiral Nicholls was awarded the C.B. in 1934 and was appointed K.C.B. five years later. In 1937, with the rank of surgeon vice-admiral, he was appointed Medical Director-General of the Navy, an appointment which he held until he retired in 1941. In 1937 he was made a Commander of the Venerable Order of the Hospital of St. John of Jerusalem, and in 1940 he was elected a Fellow of the Royal College of Surgeons of England. He was an Honorary Physician to the King from 1935 to 1952. A year after his retirement he returned to take charge of the Royal Navy Auxiliary Hospital at Kilmacolm, and remained there until his final retirement in 1946.

Admiral Nicholls was a tall, handsome man. He possessed a pleasant manner, and was always calm and unflurried. This stood him in good stead when he had to cope with the difficult problem of medical organization in the early years of the war. He was a very good tennis player, and represented the Navy at tennis in 1917. He was also a first-class golfer. Throughout his whole career he took a keen interest in all Service activities. In 1905 he married Hilda Boys Curry, and a large number of friends will remember the pleasant atmosphere and hospitality of their home. He is survived by Lady Nicholls and his two married daughters, and to them we extend our deepest sympathy.

PHILIP HAMILL, M.D., D.Sc., F.R.C.P.

Dr. Philip Hamill, for many years lecturer in pharmacology and therapeutics at St. Bartholomew's Hospital Medical School, died on March 4. He was 75 years of age.

Philip Hamill was born on October 15, 1883, and was educated at Trinity College, Cambridge, where he obtained a first-class in both parts of the Natural Sciences Tripos in 1905–6. At Trinity College he gained the Coutts Trotter research studentship in physiology and a major scholarship, and while still at Cambridge took the London B.Sc. in 1906, with first-class honours in physiology. Going on to St. Bartholomew's Hospital with an entrance scholarship to receive his clinical training, he qualified M.R.C.S., L.R.C.P. in 1910, in which year he proceeded to the D.Sc. Elected a Member of the Royal College of Physicians of London in 1912, he was admitted a Fellow of the College seven years later. In 1913 he was granted the Cambridge M.D. After qualification he held the appointments of house-surgeon at the Royal Halifax Infirmary, pathologist at the City of London Hospital for Diseases of the Heart and Lungs, and house-physician at St. Bartholomew's Hospital

Dr. Hamill settled in practice in the West End of London shortly before the outbreak of the first world war in 1914, and from then he began what was to be a long association with several London hospitals. He became assistant physician to the Metropolitan Hospital, in the Kingsland Road, to the National Hospital for Diseases of the Heart, Soho, and to St. Andrew's Hospital, Bow, in due time becoming full physician at all three hospitals. He was also consulting physician to St. Joseph's Hospice, Hackney, over a long period, and, after his retirement, became consulting physician to the Metropolitan and St. Andrew's Hospitals and to St. Nicholas's Hospital, Plumstead. For the greater part of his professional life he was lecturer in pharmacology and therapeutics at St. Bartholomew's Hospital Medical School. He was secretary of the Pharmacopoeia Committee of the General Medical Council from 1925 to 1928, and in 1928–9 acted as secretary of the Pharmacopoeia Commission until the late Dr. C. H. Hampshire assumed office. After serving as one of the honorary secretaries of the Section of Therapeutics and Pharmacology of the Royal Society of Medicine for some years, he became a vice-president and, later, president of the section. The General Medical Council in 1952 appointed Dr. Hamill as visitor of examinations and medical schools in the subjects of pharmacology and therapeutics. In the British Medical Association he served as a vice-president of the Section of Therapeutics and Pharmacology when the Association held its Annual Meeting at Cardiff in 1928, and at the Centenary Meeting in 1932 held similar office. His elder brother is Dr. J. M. Hamill, and his sister is the wife of Dr. G. E. Beaumont.

D. P. McDONALD, B.M., F.R.C.S.Ed.

Lieutenant-Colonel D. P. McDonald, I.M.S.(ret.), formerly professor of surgery in Rangoon University, died at Goudhurst, Kent, on February 26. He was 71 years of age.

The son of the Rev. Walter Percy McDonald and of Mathilde Auguste Rodatz, Donald Percy McDonald was born on March 13, 1886. His mixed Scottish, Polish, and German ancestry accounted for his most distinguished appearance and his ruthless efficiency, curiously modified by an artistic temperament. A foundation scholar of Bradfield College, he went up to Oriel College, Oxford, where he took his arts degree in 1908 and his B.M., B.Ch. in 1912, having done his clinical work at St. Thomas's Hospital. He was always interested in classical literature, particularly Latin verse, and while an undergraduate he attracted the attention of Sir William Osler and spent much time in the Osler family circle.

After graduation McDonald went back to Oxford and held resident surgical appointments there for five years. During that time he acquired great surgical skill and experience, but devoted his spare hours to artistic pursuits and Latin verse, eschewing the examination hall and the study for higher diplomas. In 1917 he took a temporary commission in the R.A.M.C. and was posted to Cairo as a surgical specialist and also as deputy to the senior consulting surgeon. In these positions his outstanding surgical skill was put to good use. He became, in addition, personal staff surgeon to Field Marshal Lord Allenby, who, in an autograph letter, strongly recommended him for a regular commission in the I.M.S., which he obtained in 1920. Throughout his service his late age of entry and unwillingness to take a higher qualification proved a hindrance to advancement, and for 15 years he remained on the military side of the service, although he was for some years staff surgeon, Bangalore, where he was able to do much useful surgical work.

Elected F.R.C.S.Ed. in 1929, he came into his own six years later when he was appointed professor of surgery in

Rangoon University. He combined a high degree of diagnostic ability with the manipulative skill of a real artist, and his operations were a joy to watch. In 1941 he had to retire on account of age but was immediately re-employed as consulting surgeon to the Army in Burma. A breakdown in health necessitated evacuation to India for an operation in 1942, and he never resumed active surgical work.

From 1942 to 1944 McDonald was director of production of surgical instruments and appliances in the Department of Supply of the Government of India. In that period when import of surgical instruments from abroad was impossible and demand growing at a fantastic rate, McDonald did noteworthy work. In 1944–5 he was attached to the office of the Director-General of the I.M.S. to assist in the organization of medical reconstruction in India and to collect material for historical and other government reports. In 1946 he joined the India Office medical board as an additional member and was carried over to the Commonwealth Relations Office establishment in 1947. Later he became a member of one of the Lord Chancellor's appeal boards. He wrote *Surgeons Twoe and a Barber*, a history of the I.M.S. from 1600 to 1947, which was published in 1950, and contributed many articles, vignettes, and commentaries to historical journals. He also wrote and had performed plays for the stage, and to the end was a devoted Latinist. For some years increasing coronary insufficiency took a steady toll of his active hours, but he bore his increasing infirmities with resolution. Our sympathy goes to his widow. There were no children.

REGINALD LAWRENCE, M.D., D.P.H.

Dr. R. Lawrence, formerly an assistant county medical officer in the West Riding of Yorkshire, died some months ago at Leeds, at the age of 81.

Reginald Lawrence was educated at Sandbach School, Cheshire, and Manchester University, where he graduated M.B., Ch.B. in 1900, having previously studied law for a short time. After proceeding M.D. in 1902 with a thesis on "The Brain and Spinal Cord in Chronic Arsenical Poisoning," he became pathologist to the Christie Hospital, Manchester. Having obtained the D.P.H. in 1905 he was an assistant medical officer in Blackburn for a time, and was then appointed assistant school medical officer to the Cheshire County Council. He acted also as tuberculosis officer to the City of Chester. In 1916 he became assistant to the bacteriologist of the Irish Command (R.A.M.C.) at Trinity College, Dublin, and subsequently he worked as bacteriologist to the Curragh Camp. At this time he published several papers on cerebrospinal fever. In 1920 he was appointed assistant medical officer of health to the West Riding of Yorkshire. He was specially interested in the maternity and child welfare side of the work and was responsible for many worth-while improvements in the service. His knowledge of public-health matters was wide, and he was much in demand as a lecturer.

On his retirement from the service of the county council Dr. Lawrence did not retire from medicine, but occupied himself in general practice in many parts of Yorkshire, finally spending several very happy years in practice in Pontefract. At this time he began to feel the crippling effects of osteoarthritis of the hip-joints. When eventually he retired from medicine at the age of 78, he assiduously looked after his wife, who was in failing health. Eventually he moved to Leeds, and was looked after by his daughter-in-law, of whom he was very fond. A scholarly, kind, and witty man, he found happiness and tranquillity surrounded by his books, for combined with his professional attainments he had a deep love of the literatures of Europe, ancient and modern. His wife survived him by only six weeks. He leaves four sons, of whom three are doctors—one a gynaecologist, one a radiologist, and one an anaesthetist.

W. N. P. writes: It is said that in a man's later years he acquires the face he deserves. Had one sat opposite Reginald Lawrence in a railway carriage, glancing furtively at him, one would have felt drawn to this picturesque figure with the broad, high forehead and calm, philosophic mien, capped with an abundant mass of unruly hair. If one had broken the ice and got into conversation with him, one would have found a quiet, courteous gentleman behind this imposing exterior, whose every sentence breathed culture and thought. Lawrence was a scholar and a precisian with the saving grace of humour, which prevented him being a pedant. But he was not merely a visionary. He brought skill and talents of organization to his life's work, and it was his determination to keep in touch with clinical medicine that brought to me a rare and prized friendship, as on many occasions I had the privilege of his help when he chose to spend part of his annual leave as my locumtenent. His knowledge of the literature of this country was much beyond the average, and his acquaintance with Latin and Greek led to a serious study of these in his happy retirement. His last years were marred with disabling arthritis, which did not, however, quench his spirit, and his end was mercifully speedy, in the full enjoyment of living.

JOHN PEARSON, M.B., Ch.B.

Dr. John Pearson, who was in general practice at Bonnybridge, Stirlingshire, for over 40 years, died at Falkirk and District Royal Infirmary on December 26, 1958. He was 77 years of age.

John Pearson was born in Glasgow on November 18, 1881, and graduated M.B., Ch.B. from Glasgow University in 1905. For a period of five or six years after graduation he worked mostly in the west of Scotland as a locumtenent and as an assistant before becoming assistant to Dr. John Young at Bonnybridge in 1911. In 1915 he became a partner, and shortly afterwards enlisted in the R.A.M.C. for service in the first world war, during which he was for some time in the Middle East. When the war was over he came back to Bonnybridge and settled into his former routine. He married after his return from the Forces, and two children were born. Unfortunately the elder died as the result of a tragic accident, and his surviving son is now a dental surgeon in the Royal Army Dental Corps. In the early 1930s Dr. Pearson was himself nearly electrocuted, and his wife died. Despite these calamities he continued his work, and also took part in many other activities. A keen freemason, he was grand master of the Lodge Dolphin (Bonnybridge) and senior warden of the Grand Provincial Lodge (Stirling). At the same time he took a very active part in the work of the St. Andrew's Ambulance Association, and in 1925–6 was president of the Stirling Branch of the British Medical Association. During the second world war he very ably ran the local first-aid group, assisted by his second wife, who survives him, and to whom our deepest sympathy is extended. To all who really knew him the death of John Pearson is a great loss. In his younger days he was a very hard-working and able doctor, with a pawky sense of humour which made of him an extremely charming man. After his accident his activity was much restricted. By the time of his retirement in 1953 he was carrying on under great difficulty, and it was a source of great regret to him when he had to stop work. Not many of his contemporaries are alive to-day, but those who are must have many cherished memories of this delightful personality.—A. Y.

E. A. W. HOUGHTON, M.B., Ch.B., D.M.R.D.

Dr. Eric Houghton, registrar in diagnostic radiology to the United Bristol Hospitals, lost his life on February 21 while climbing a peak in Snowdonia. He was 31 years of age.

Eric Alfred William Houghton was born on April 25, 1927, and studied medicine at Bristol University, where he

graduated M.B., Ch.B. in 1950. He held the appointments of house-surgeon at Bristol Royal Infirmary, and senior house officer at Frenchay Hospital, Bristol, and Hawkmoor Chest Hospital, Bovey Tracey. At Frenchay Hospital he worked in the department of neurological surgery, and while there contributed an article to this *Journal* in 1953 on electrolyte imbalance after operation for pituitary tumour. From 1954 to 1955 he was medical registrar at Southmead Hospital, Bristol, and three years ago he was appointed registrar in diagnostic radiology to the United Bristol Hospitals, working mainly at Southmead Hospital. He obtained the D.M.R.D. of the English Royal Colleges in January of this year. He leaves a widow and one son and one daughter.

MR. ALLAN HULME writes: The tragic death of Dr. Eric Houghton in a climbing accident in North Wales comes as a great blow to his friends and colleagues. After a number of years in hospital appointments and general practice he had entered the specialty of radiology with characteristic energy and enthusiasm. A man of very varied interests and talents, he was a connoisseur of wine and a prominent supporter of the campaign against nuclear weapon tests. One knew him best perhaps in the intimacy and companionship of the hills. He was a determined and courageous mountaineer who earned the highest regard and affections of his companions. The profound sympathy of all his colleagues, friends, and climbing associates extends to his widow and two young children in their grievous loss.

DR. JOHN NAISH writes: Eric Houghton was a man who impressed everyone with his sincerity. As a student and a house officer in the Bristol hospitals his work was outstanding because so thorough and so complete. His scholarly aptitude and adventurous mind led him early towards original work, and latterly, since he took up the practice of radiology, he engaged in many research projects which meant countless hours of accurate study. His rapid appreciation of the possibilities and limitations of the radiological techniques he was using, and his clear insight into the ways in which these could be improved, certainly impressed more than one clinician, and I know that he was held in very high regard by his seniors in radiology, who were quick to realize that they had as a student and a junior a man whose work showed all the signs of great promise for the future. Had he lived he would, I am sure, have fulfilled that promise, for he was full of energy; and the zest for knowledge would never have deserted him. The adventurous spirit, which was disguised behind a shy exterior, led him to climbing and other sports, to all of which he brought his full powers. As a student, although severely myopic, he played rugby with tremendous fire and courage. Latterly mountain climbing became his great passion. It is sad that one with so many gifts is lost to the profession while still so young, but the greatest sadness must be for his widow and young family, to whom all his many friends will wish to offer their deepest sympathy.

H. E. R. STEPHENS, O.B.E., M.B., F.R.C.S., D.P.H.

Surgeon Rear-Admiral H. E. R. Stephens, who had had a long and distinguished career in the medical service of the Royal Navy, died on February 18, aged 76.

Horace Elliot Rose Stephens was a son of the Rev. Horace Stephens, M.A., rector of Handley, Cheshire. He was born at Chester on January 4, 1883, and was educated at Christ College, Brecon, Manchester University, and the London Hospital. In his undergraduate days he played rugby football for Manchester University, and on different occasions represented both Cheshire and Lancashire at the game. He graduated M.B., B.S. from London University in 1907. At the Manchester Royal Infirmary, where after graduation he worked as a house-surgeon, he won the prize for clinical medicine. He was also for a time junior demonstrator of anatomy at the University of Manchester. He entered the Royal Navy in 1910, and in the first world war served in H.M.S. *Eclipse*, H.M.S. *Lion*, and at the Royal Naval Hospital, Plymouth. In H.M.S. *Lion* he was present at the battle of the Dogger Bank and the battle of Jutland, and for his services there was mentioned in dispatches. He was appointed O.B.E. in 1919 and awarded the Croix de Guerre avec Palmes.

He took up surgery as a specialty, and in 1920 was admitted to the F.R.C.S. In that year, at his own expense, he made an extensive tour of the surgical clinics in the United States, where he became very friendly with the Mayo brothers. He served in ships in the Atlantic, Mediterranean, China, North America, and the West Indies stations, and also at different times was surgical specialist at Haslar, Plymouth, and Chatham. In 1935, after an illness, he gave up surgery and, rather unexpectedly, took over the position of professor of hygiene and director of medical studies at the Royal Naval Medical School at Greenwich—he had taken the D.P.H. a good many years before. He carried out his duties there with his usual distinction and did very useful work in connexion with the promotion courses for medical officers in the years before the second world war.

In 1939 he was promoted to the rank of surgeon rear-admiral, and on the outbreak of the second world war went to Scotland, where he had the very difficult task of organizing the Royal Naval Auxiliary Hospital at Kingseat, and supervising the other numerous smaller medical establishments which were started during the war. He retired in 1943, and after the war lived at Trearddur Bay, in Anglesey, where he was a keen golfer and much loved by the local people. When president of the United Services Section of the Royal Society of Medicine in 1933, he delivered a most interesting address entitled the "Influence of Wars on the Craft of Surgery." He was the author of many other papers, including one on surgical experiences at the Battle of Jutland, and he wrote the chapter on "Surgery in a Fighting Ship" in Keen's *American Textbook of Surgery*. In 1935 he served on the B.M.A.'s Committee on Physical Education, and on two of its subcommittees.

Horace Stephens was a conscientious and zealous officer who in his time was an ornament and example to the medical officers of the Royal Navy. They, as well as the R.N.V.R. officers who served with him during the war, will remember him with pride and affection. In 1911 he married Frances Mary Butt and had one son, Captain H. A. P. Stephens, and a daughter, Mary, who is married to Surgeon Rear-Admiral R. W. Mussen.

RUSSELL V. STEELE, M.B., B.S.

Dr. Russell V. Steele, who was in general practice for many years in London, died suddenly on February 9, aged 70 years.

Russell Vyvyan Steele, who was born on August 28, 1888, at Hemel Hempstead, Herts, was a member of a medical family, fourth in the line of general practitioners. The eldest son of Dr. Russell Steele, of Reigate and Hemel Hempstead, and nephew of Sir David Bruce, he started his education at Berkhamsted School, and then went on to Epsom College, where his father had been one of the first pupils. He received his medical training at his father's old hospital, University College Hospital, and later at the College of Medicine, Newcastle upon Tyne. After graduating M.B., B.S. from the University of Durham in 1913, he became house-surgeon and house-physician at the West London Hospital, and was then appointed resident surgical officer of the Schiff Home of Recovery, Cobham, at a time when the first Belgian wounded and casualties from the B.E.F. were being admitted. In March, 1915, he received a commission in the R.A.M.C. and saw service in France, where he experienced trench warfare (being attached to the 84th Field Ambulance), and later at Salonika. Invalided home with dysentery, he was discharged, but

after his recovery he rejoined the R.A.M.C. and was posted to Gosport.

In 1919 Russell Steele took up general practice at Devizes, Wilts, where he was attached to the cottage hospital, and three years later came to London to practise at Gloucester Gate, Regent's Park. He had a sound knowledge of medicine, and during his professional life he witnessed the introduction of many new methods of treatment. For over thirty years he took an active part in the work of the St. John Ambulance Brigade, finally being appointed area commissioner of the central area of London. In 1951 he was created a Knight of the Venerable Order of St. John of Jerusalem. In later years he took great interest in the Legion of Frontiersmen, of which he was chief medical officer. He was a Freeman of the City of London, a Yeoman of the Society of Apothecaries, and a member of the Royal United Services Institution.

Russell Steele was a man of many interests and had a good knowledge of several languages. An authority on matters of military history and military uniform, he was a member of the Army Historical Research Society and other similar societies and the author of many articles on the history of military uniforms. He had a notable collection of old coloured military prints, including four very fine specimens presented to him on his retirement from the St. John Ambulance Brigade. Well known for his rapid pen-and-ink sketches, he very rarely wrote a letter without some embellishment in the form of a military sketch. He recently became a member of the Medical Arts Society.

Russell Steele was a great opponent of State medicine, believing that a doctor should be free as an individual and responsible only to his patients. In this he was upholding the tradition handed down to him by his great-grandfather. As one of his patients had said, "Dr. Russell Steele was one of the 'old school'—a true friend to his patients and much beloved, and he will be sadly missed." His sudden death came as a great shock and grief to his relatives and to his many friends and patients.

WILLIAM ARMITAGE, M.B., Ch.B.

Dr. William Armitage died at his home at Cumnock, Ayrshire, on January 9, at the age of 80 years.

A native of Greenock, William Armitage was born on April 2, 1878, the son of a pharmaceutical chemist. He was educated at Greenock Collegiate School, later graduating M.B., Ch.B. at Glasgow University in 1902. After a period as house-surgeon at Greenock Infirmary, he went to Cumnock in 1904 as assistant to the late Drs. J. G. Kerr and James McQueen. In due course he was taken into partnership, and at the time of his retirement, in 1947, was the senior member of the partnership. He was a keen lecturer and demonstrator in first aid and was a promoter of the formation of the Surgeons' Fund in Cumnock, a contributory scheme for the dependants of miners. He was closely connected with the Bute Hospital, and was medical officer for the burgh of Cumnock and Holmhead. The variety of the modes of transport used by Dr. Armitage—from travelling to outlying farms by horse-drawn carriage up to the use of the modern car—emphasizes the wealth of experience gained by steadfast service to the public, often under conditions of severe physical and mental strain. There are many who mourn his passing. He leaves a widow, three sons, and a daughter. Two of his sons are in the medical profession.—H. S.

ELWYN PUGH-JONES, L.M.S.S.A.

Dr. Elwyn Pugh-Jones, who was in general practice at Whitton, Twickenham, for nearly a quarter of a century, died on January 17, after two years of steadily deteriorating health. He was 50 years of age.

Elwyn Pugh-Jones was born on September 11, 1908, and qualified L.M.S.S.A. from Guy's Hospital in 1933. After holding house appointments at the Royal Hospital, Richmond, he joined Dr. Sydney Darke and Dr. Wilfred Jewitt in general practice in 1935. He made his home in the then newly developing district of Whitton, in the borough of Twickenham, and there he lived and worked for the rest of his life. He rapidly attracted a very large practice, and when war came in 1939 he had to run it with very little assistance. He was constantly in demand as a police surgeon and was very popular with the local members of that force. When illness forced him to resign the police appointment in 1957 after 21 years' service he was presented with a large, suitably inscribed picnic hamper by the men of the local division. All the activities of the South Middlesex Division of the British Medical Association received his full support, and he was their representative on the Metropolitan Counties Branch Council for several years.

Pugh-Jones enjoyed a very happy home life, but his restless energy never let him relax for long, and the constant work in his practice, while it earned him the gratitude of thousands of his patients, undoubtedly contributed to his early death. At his memorial service his many patients and friends filled the Whitton Baptist Church to capacity and overflowed on to the pavements outside. Pugh-Jones was a big man, with a modest but downright approach to life. He played a useful game of rugger in his student days and in later life nothing gave him more pleasure than to take a large party of friends from Wales to the Welsh match at Twickenham and to entertain them at his home afterwards. He will be missed by a very large circle of friends, colleagues, and patients, and their sympathy will especially be extended to his widow, three daughters, and son.—D. A. D.

W. H. F. OXLEY, F.R.C.O.G., M.R.C.S., L.R.C.P.

The obituary of Dr. W. H. F. Oxley was printed in the *Journal* of February 14 (p. 443).

D. G. W. C. writes: It was with a very real feeling of sadness and personal loss that I read of the death of Dr. W. H. F. Oxley at the age of 83. For 26 years Dr. Oxley was untiring in his efforts to further the cause of obstetrics in general and the name of the East End Maternity Hospital in particular, which was very dear to his heart. For most of that time he was entirely responsible, without any medical assistance whatsoever, for all of the emergency work connected with the hospital, this in spite of the fact that he was engaged at one and the same time in the running of a busy general practice at Poplar. During those 26 years he saw the East End Maternity Hospital increase in size from a mere handful of beds to a fully equipped maternity hospital. What began as almost a "one-man show" was developed by Dr. Oxley into a maternity hospital of 62 beds, staffed by consulting obstetricians, surgeons, physicians, paediatricians, anaesthetists, pathologists, registrars, and housemen, and supported by as good a staff of sister-midwives as it has ever been my good fortune to meet.

When he decided to retire in 1948 with the advent of the National Health Service, Dr. Oxley had indeed reached the very top of his profession, and it is a truism that his name was known internationally as a confirmed exponent of conservative midwifery. This quotation from *Operative Obstetrics* (Munro Kerr and Chassar Moir, p. 34, fifth edition) illustrates his unshakable point of view.

"It is certainly disconcerting to have one's faith in perchloride and biniodide of mercury shaken; on the other hand, one cannot get away from the fact that the records of all maternity hospitals and domiciliary services in which a strict, but simple antiseptic, ritual is enforced, and perchloride or biniodide of mercury solution is employed freely and in sufficient strength (1:500–700), show excellent results both as regards mortality and morbidity. This has been the experience of obstetric surgeons for the last 50 years, as is evidenced by the results presented by Boxall for the Lying-in Hospital, York Road; by Smyly for the Rotunda Hospital in the late 'nineties' of last century; by Tweedy during his mastership early in this century; and recently by Oxley for the

East End Maternity Hospital, London. And, let it be noted, without the employment of gloves and masks."

The excellence of Dr. Oxley's work, which was reflected by the equally excellent reputation of the East End Maternity Hospital, culminated in the award of foundation membership of the newly constituted British (now Royal) College of Obstetricians and Gynaecologists in 1929. Two years later Dr. Oxley was elected to the Fellowship of the College, and was, I have always understood, the first general practitioner to be so honoured. His work as chairman of the committee which investigated the causes of maternal deaths was later recognized as being materially responsible for the magnificent reduction in the maternal mortality rate to its present low level. Quite apart from this, he achieved a wide reputation both as a stimulating teacher of obstetrics and as the author of many articles in the medical press. Apart from his purely obstetric work, he won repute for his investigations into industrial diseases, notably lead-poisoning, in which he was one of the first to demonstrate the diagnostic importance of punctate basophilia. In this field, also, Dr. Oxley had the satisfaction of seeing many of his recommendations put into practice.

I will always remember my earliest association with him, when he was my co-examiner on the very first occasion when I officiated in that capacity for the Central Midwives Board. Frankly I was surprised when a slightly built, bespectacled man in his late sixties, with a neatly trimmed white moustache and a self-effacing smile, sat down beside me. From his reputation I had expected somebody large and forceful. But Dr. Oxley's apparently frail frame was misleading. His whole life was devoted to the knowledge and advancement of the obstetric art, and as I very soon learned during the course of that first examination, nothing but the best was, for him, good enough.

Dr. Oxley was typical of the very best in what is nowadays called the "old-fashioned family doctor." Quiet and gentle, with untiring keenness and an unfailing interest in both his patients and "his" hospital, Dr. Oxley's delightful personality impressed itself upon all of us who were later to be associated with him as colleagues. Everybody loved and admired him, and I know of nobody more deserving of the epitaph: "Well done, thou good and faithful servant."

H. M. D. SHEPHERD, M.D., F.R.C.P.Ed.

The obituary of Dr. H. M. D. Shepherd was printed in the *Journal* of February 28 (p. 589).

A. J. D. writes: I had not met Hugh Shepherd until the last two weeks of his life, but on behalf of those of us in Exeter who were privileged to know him during that short time I would like to add a note of appreciation to your notice and to join in J. W. T.'s expression of sympathy with his widow. He gave us an impressive example of that particular degree of fortitude demanded of the physician who finds himself suddenly, and without warning, in the grip of an illness of which his own knowledge enables him, like Keats, "to judge every change in himself." After days of initial anxiety he seemed set on the road to recovery, thus making particularly keen the disappointment of his sudden and fatal relapse.

C. C. BARNARD, B.A., F.L.A., F.I.L.

Mr. C. C. Barnard, librarian of the London School of Hygiene and Tropical Medicine since 1921, died on March 6 as the result of a road accident.

Cyril Cuthbert Barnard was born at St. Margaret's, Twickenham, Middlesex, on July 23, 1894, and educated at the Stationers' Company School and the University of London, where he graduated B.A. in 1922. At University College, London, he attended the School of Librarianship and was awarded its Diploma in 1924. He joined the Library Association in 1913, being elected a Fellow in 1925.

Cyril Barnard began his career in librarianship at the Reform Club in 1913. From 1914 to 1918 he was assistant librarian at the Royal Society of Medicine and from 1918 to 1921 acting librarian of the Wellcome Historical Medical Library. In February, 1921, he was appointed the first full-time librarian of the Tropical Diseases Library, which later passed to the London School of Hygiene and Tropical Medicine. When this School moved to its present site in Keppel Street in 1929, he had the most modern medical library building in the country, and one in which many of his ideas and much of his experience were incorporated. Being dissatisfied with existing codes of classification for medical libraries, he set out to devise a new scheme which, while designed for the special needs of his own library, would be suitable for general use. The result, his *Classification for Medical Libraries*, gained him the honours diploma of the Library Association (1931), and it was published in 1936. A revised and enlarged second edition was published in 1955. In 1952 he spent some months reclassifying the library of the World Health Organization according to his scheme, and while in Geneva acted as chairman of a seminar on training for medical librarianship. He was a pioneer in the instruction of students in the use of the library and was instrumental in having this subject included in the curriculum at the School of Hygiene.

He served on the council of the Library Association for some years and was secretary of its University and Research Section for a long period. When the Medical Section was formed in 1947 he was the obvious choice as its first chairman. He also served on the committee responsible for organizing the First World Congress on Medical Librarianship, 1953.

A member of the Society of Friends, Cyril Barnard devoted much of his leisure time to the charitable and humanitarian work of the Quakers. He leaves a widow, a son, and a daughter.

Medico-Legal

LEGAL ADVICE SCHEME

[FROM OUR LEGAL CORRESPONDENT]

After a ten-year wait, Section 7 of the Legal Aid and Advice Act, 1949, has now been brought into force by Statutory Instrument No. 46 of 1959. Those who attribute the increase in litigation on medical negligence at least in part to the Act of 1949 will be concerned about the new scheme.

Section 7 is the operative Section of the Act which deals with "advice" as opposed to "aid." It provides for legal advice, consisting of "oral advice on legal questions given by a solicitor employed whole-time or part-time for the purpose," to be made available in England and Wales for any person. Advice includes help in preparing an application for legal aid, but is restricted to advice on questions involving English law. That the advice is "oral" is not to prevent the giving of a written note if the solicitor thinks the person advised will need it. Normal professional privilege from disclosure and the normal professional obligation not to advise negligently are expressly applied to such advice by Subsection (10).

Operation of the Scheme

Subsection (7) provides for the making of regulations, and Statutory Instrument No. 47 of 1959, which came into effect on March 2, like No. 46, under the title Legal Advice Regulations, 1959, has been made pursuant to that Subsection. Under these regulations the Law Society is required to prepare panels of solicitors in ordinary practice who are willing to give advice under the scheme. Anyone who is not under 16, and who qualifies financially by satisfying the solicitor that his capital does not exceed £75 and that his income after allowing for specified deductions does not exceed £4 10s. in the week of the application, is entitled to legal advice if he can also satisfy the solicitor that

he cannot obtain it in the ordinary way. Unless he is receiving National Assistance he will have to pay half a crown per interview, and the solicitor is not to give him more than 1½ hours on any one legal question without prior authority from his Law Society Area Committee. The solicitor is to get £1 per half-hour from the Legal Aid Fund, and the half a crown is to be collected by him from the client on account, but an Area Committee in authorizing extra time may also authorize extra payment.

A solicitor to whom application is made can entrust the problem to his partner or to a "competent and responsible representative employed in his office." He can also refuse an application, or refuse advice for good cause which he need not explain to the applicant though he must provide specified information about it to the Area Committee. There are also provisions for dealing with repeated applications and with false statements.

As in the Legal Aid Scheme, the aim has been to avoid interference with the solicitor–client relationship but to subsidize the client according to need. The aim has been successfully achieved under the Legal Aid Scheme because the need, and the amount of subsidy, is in effect assessed not by the solicitor but by the National Assistance Board. Whether the solicitor–client relationship will successfully survive a situation which involves an on-the-spot means test of client by solicitor remains to be seen.

Will it Increase Medical Litigation?

Some think that the Legal Advice Scheme will reduce the turnover under the Legal Aid Scheme; that it will be preventive medicine; and that people going for advice under the scheme will save themselves from getting into the messes to extract themselves from which they would apply for legal aid. But the great majority of legal aid applications relate to divorce, and the minute proportion which relate to medical negligence cases are likely to be as little affected by legal advice as the divorce applications.

EMPLOYER'S LIABILITY FOR DEFECTIVE TOOLS

[FROM OUR LEGAL CORRESPONDENT]

On January 28 the House of Lords delivered judgment in an appeal upon the following facts. In March, 1953, Mr. James Davie, a maintenance fitter employed by New Merton Board Mills Ltd., was knocking out a metal key with a punch and hammer. At the second blow of the hammer a piece of metal flew off the head of the punch and injured his eye. The punch, which his employers had provided, although apparently in good condition, was excessively hard. They had bought the punch from a reputable firm of suppliers, and it was agreed that their system of inspection and maintenance was not at fault.

Mr. Davie sued both his employers and the manufacturers for negligence. The trial judge gave judgment for Mr. Davie for £2,030 against both defendants. The manufacturers did not dispute the finding that they had been negligent, but the employers appealed. A majority of the Court of Appeal held that the employers were not liable, as they had exercised reasonable care in their choice of suppliers and in their inspection of the goods when bought. Mr. Davie then appealed to the House of Lords, where the majority decision of the Court of Appeal was upheld. Their Lordships stated that their decision would have been the same if the punch had been bought direct from the manufacturers and not through suppliers (*The Times*, January 29).

Implications for Medical Practice

If the decision at first instance had stood an employer would be, in effect, an insurer of his employees' safety, liable for every injury resulting from defective tools or equipment, even if the defect was latent, and even if the employer had exercised reasonable care. The decision of the House of Lords in this case, however, means that the liability of an employer towards his workmen is now based on the general principles of the law of negligence. The law of negligence has always applied as between a hospital authority and a patient, or between a doctor and his patient. But now these same principles will apply between a hospital authority and the medical and lay staff it employs, and also between a principal in general practice and anyone he may employ. Thus if a sphygmomanometer bursts and a piece of glass lodges in the eye of a houseman using it, the hospital authority will be liable for the injury only if the hospital authority has shown a lack of care.

There may be a lack of care in the choice of the manufacturer of the instrument, or in the choice of supplier, or in the inspection and maintenance of the instrument. The duty to inspect and maintain equipment is probably the duty most easily and most often neglected. The degree of care required and the frequency of inspections depend upon what is reasonable in all the circumstances, and in assessing what is reasonable one should consider particularly the likelihood of a defect occurring, the seriousness of the injury likely to result from any defect, and the amount of effort and time required for an inspection.

The nineteenth-century principle of no liability without fault has now prevailed over the more recent view that an employer should bear all the risks of his enterprise and pass the cost on to the consumer through the price of the goods manufactured, or the charge for the service provided.

Medical Notes in Parliament

WRONGFUL DISMISSAL OF CONSULTANT

EARL WINTERTON asked the Government on March 4 if they would introduce regulations or, if that be necessary, legislation to ensure that where a court had held that a consultant or senior hospital medical officer in the Health Service had been wrongfully dismissed by a regional hospital board or board of governors of a teaching hospital he should be immediately reinstated in his original post.

The EARL OF ONSLOW, captain, Yeomen of the Guard, stated that under the Health Service Act, 1946, a statutory responsibility rested on regional hospital boards and boards of governors of teaching hospitals for the provision of specialist services in the hospitals under their control, and section 14(2) of the Act specifically reserved to the boards the power to appoint consultants and similar staff. In addition, the terms and conditions of service of hospital medical and dental staff provided that a consultant or senior hospital medical officer who considered that his appointment was being unfairly terminated had the right of submitting his case to the Minister of Health before a decision to terminate the employment could be carried into effect. If, in spite of these safeguards, a consultant or other officer considered he had been wrongfully dismissed his remedy lay with the courts, which might award damages. In these circumstances the Government were not satisfied that it would be justifiable to introduce regulations or legislation for the purpose Earl Winterton suggested.

EARL WINTERTON said he was fully aware of that. He was asking the Government spokesman to deal with the situation which had arisen in a case in which a distinguished consultant was held by a court to have been wrongfully dismissed and was awarded damages. The judge made some wounding observations, not only about the hospital board but about the Ministry of Health. He asked that further consideration should be given to the matter, to avoid the possibility of a

similar case arising in future, which might easily result in great unpopularity of both the Government and the Ministry of Health. The EARL OF ONSLOW replied that he was fully aware of the case referred to. It was almost impossible that it could happen again, because the contracts now were all the same, which they were not then, as this was a take-over case from the voluntary hospitals to the Health Service. He wondered whether Earl Winterton was as fully aware of the case as he was. It was a very strange circumstance. This came about because the documents were not produced by the man concerned five years ago.

"Reaching the Stage of a Scandal"

VISCOUNT STANSGATE said the case was creating considerable concern, and was reaching the stage of a scandal. This obstetrician was dismissed. Mr. Justice Barry declared that he had been wrongfully dismissed and awarded him damages. Yet there was no means by which he could secure redress. What Earl Winterton was asking was whether, by a simple alteration of the regulation, this injustice could be remedied. The EARL OF ONSLOW replied that the doctor was operating in a voluntary hospital and was taken on with the Service when the hospital became nationalized. The trouble arose, and the doctor was dismissed by the board and told that he had a right of appeal. This was in 1952. He produced no documents of his contract for service at the time, and the then Minister thought he was not entitled to a right of appeal under his then alleged contract for service. In 1957 he produced a letter from the hospital board saying that they were taking him over on the new form of contract for service and that papers would be sent to him.

VISCOUNT STANSGATE: Does the noble Earl consider anything he has said—no doubt it is quite accurate—can excuse the case of a man who the Queen's Bench Division has declared was wrongfully dismissed and entitled to damages? The noble Earl has nothing but an explanation, which may no doubt be very good, but it does not redress what is a major grievance. The EARL OF ONSLOW: I can answer the noble Viscount quite happily. I said that if this doctor had produced this letter at the time he was dismissed by the hospital board who told him he had the right of appeal the Minister would certainly have heard the appeal. What the Minister's views would have been I cannot say. But the doctor did not produce these papers, and at the time he was thought not to be eligible for this appeal.

A General Question

LORD SILKIN said this was a general question, and was not particularly related to an individual case. The general question was that if such a thing should happen in the future, and a doctor was found to be wrongfully dismissed, could it be right that he should not be reinstated? Would the Government consider making regulations so that in such a case in future a doctor would be reinstated? The EARL OF ONSLOW said he understood that all doctors were now under this form of contract and it was almost impossible that they could be wrongfully dismissed. The possibility was now being considered of amending the regulations to enable boards, where the appointments of consultants were terminated through no fault of their own but owing to redundancy, to put these doctors into other jobs, without their having to go through the paraphernalia of answering advertisements.

Ministry's Action

VISCOUNT ALEXANDER OF HILLSBOROUGH asked, in view of the decision of the court, what steps the Ministry had taken to see that this professional man was properly rehabilitated. Had he been reappointed? Had he suffered no loss of status in his reappointment? The EARL OF ONSLOW said he understood that he had a large private practice and was also employed by a local authority on certain work. After the judgment the Minister wrote to the hospital board and said he felt there was a moral obligation, and that should this man apply in the ordinary way for any work that was going, if he was as good as any other applicant the moral obligation should weigh in his favour.

EARL BALFOUR OF INCHRYE: Has the doctor received the damages; and is the Minister now prepared to reconsider retrospectively the case of this doctor who has been wrongfully dismissed? The EARL OF ONSLOW: I understand that this doctor has received substantial tax-free damages as awarded by the judge, who at the time said there was no possibility of reinstatement. One has to remember that he was in a post which the hospital chose to divide into two. Would it really be sensible, after five years, to tip out two perfectly good men, who were doing the work admirably, and to put him in, when the judge, in this purely technical case, awarded him some £7,000 damages and he is earning a good living in his own profession?

EARL WINTERTON: Will you ask the Minister to give full consideration to taking every step to avoid similar cases arising in future? The EARL OF ONSLOW: I can assure the House that is certainly being done at the moment.

Departmental Committee

VISCOUNT ALEXANDER OF HILLSBOROUGH: Would it not be wise, in view of the extent of the Service, and the doubts about these matters, to have a departmental committee to inquire into what should be the proper basis of discipline of professional men, and to submit a report to Parliament? The EARL OF ONSLOW: That is something of which the Minister will obviously take notice.

MENTAL HEALTH BILL

The Mental Health Bill standing committee have got past the hurdle of compulsory admission to hospital. In two more sittings on March 3 and 5 they decisively rejected appeals for the retention of the justice of the peace procedure, and moved on to discuss the compilation of the list of psychiatrists approved to sign admission orders and the limitation of emergency action to observation.

Appeals to Retain the J.P.

Clause 27 contains general provisions relating to applications for admission to hospital compulsorily "for observation or for treatment." Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) moved an amendment to delete the condition "or for treatment." He claimed emphatically that the serious responsibility of depriving a person of his civil rights and liberty should not be forced on the medical profession by law. The justice of the peace, as the representative of the civil authority, should retain his existing responsibility and act as a safeguard against wrongful compulsory detention. He cited in support the views of the National Council for Civil Liberties, and added to them the argument that not all general practitioners were mature men of wide knowledge and experience; some who might have to make these recommendations might be young and inexperienced, possessing little knowledge of psychiatry, and some—even senior psychiatrists—might be foreigners without sufficient understanding of British ways to guide them on what was abnormal behaviour. He also feared that there would be a serious danger of the doctor–patient relationship being harmed.

The MINISTER came out equally emphatically against the amendment. It shook the structure of the Bill to its foundations, he said, and would irreparably damage it. One of its central features was to replace the judicial order by the tribunal procedure, with two doctors making independent medical assessment. The present judicial order procedure belonged rather to the administrative than the judicial functions of the J.P.; and to crown its disadvantages the J.P. was acting without a judicial colleague or a justice's clerk. In the last analysis what was required was a medical judgment.

Both the B.M.A. and the Royal Medico-Psychological Association had commented on the new system, and each had welcomed the elimination of the J.P. procedure. Since, in the last resort, it was a medical analysis that was required he could see no advantage to the patient in the doctor being able to shelter behind a magistrate, and no real advantage to the doctor either. The inescapable fact was that a large part of the responsibility must be on doctors, because it was a medical judgment.

Amendment Defeated

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) saw as the root of the matter that some psychiatrists simply did not want this responsibility, which in their opinion was a social and not a medical responsibility. Interference with the doctor–patient relationship he dismissed as a red herring, raised by a small section of the medical profession. Dr. DONALD JOHNSON (Carlisle, Con.) expressed much sympathy with Dr. Broughton's views. Decisions on deprivation of liberty were a social rather than a medical judgment. Mr. NORMAN DODDS (Erith and Crayford, Lab.) took much the same view. Mrs. E. M. BRADDOCK (Liverpool, Exchange, Lab.), who was a member of the Royal Commission, reproached them with being unable to appreciate the new approach embodied in the Bill, and denied that doctors wanted to detain patients for any reason except that treatment was necessary.

Dr. BROUGHTON stuck to his point that it was the doctor's function to advise on compulsory detention, and that of a civil authority to authorize it. He insisted on a division, but found only one supporter (Mr. Dodds) and 26 against him.

Approved Practitioners

On Clause 28 (general provisions as to medical recommendations), Mr. K. ROBINSON moved an amendment to transfer from the local health authority to "the Minister, after consultation with regional hospital boards and boards of governors" the approval of practitioners as having special experience in mental disorders who should make one of the two medical recommendations required for compulsory admission. He argued that the local health authority was not in a position to know what doctors in the area were competent to do this work. The people with most knowledge of that were the regional hospital boards. But there was something to be said for applying common standards over the country, and for that reason he would place the duty of drawing up lists on the Minister, after consultation with the boards.

Mr. WALKER-SMITH took the view that the statutory duty of giving approval should remain with the local authority, in accordance with the views expressed by the Royal Commission, but promised to take power under the regulation-making clause (52) to issue regulations giving general guidance to authorities on the qualifications and experience for which they should look. He was attracted by the idea put forward by the Royal Medico-Psychological Association that the authorities should act on the advice of joint committees composed of medical representatives of the local authorities and the hospital authorities. Because of the complicated structure of the service this could best be done by regulation. Mr. ROBINSON withdrew his amendment.

Emergency Procedure

On Clause 29 (application for admission in case of emergency) Mr. ROBINSON moved another amendment which he took to a division. This was to delete the phrase "or for treatment" from subsection (1) providing for emergency applications for observation or for treatment in cases of urgent necessity. Emergency procedure, while necessary, should be used sparingly, he said, and should be limited to an observation procedure, and not treatment. Dr. D. JOHNSON, supporting the amendment, said that if the phrase remained there was a risk that the observation procedure would become a dead letter.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) said that to omit treatment would be to affect the very category who when admitted immediately needed treatment, if it was only nursing and sedatives. Dr. BROUGHTON said that if the amendment was accepted, as he hoped it would be, there would be nothing to prevent immediate treatment being given to patients, even drastic treatment. The point of the amendment was that patients should not be admitted under the 72-hours order as an immediate prelude to admission under Clause 26.

A Case for Thought

Mr. WALKER-SMITH said the difficulty was that in trying to add this additional safeguard they would inevitably bar a sound therapeutic approach. There might be cases which ought to be treated as emergency cases but were of such a class that they could not conscientiously be regarded as requiring observation because the observation would not serve any useful purpose, since all was known. There might be a case of urgent necessity demanding action, but nothing to be "observed." He would think carefully about the matter, to see how far he could go. If he could resolve the difficulty without shutting out those people he would be prepared to meet the point. The amendment was rejected by 19 votes to 10.

QUESTIONS IN THE COMMONS

Patent Medicines on Television

Mr. NESS EDWARDS (Caerphilly, Lab.) asked the Postmaster-General on March 4 what directions he had given under Section 4(5) of the Television Act, 1954, relating to the claims made for patent medicines in commercial television advertisements.

Mr. KENNETH THOMPSON, Assistant Postmaster-General: "None. The 'Principles for Television Advertising' contain the rule that the advertising of medicines and treatment must comply with the basic standard of 'The British Code of Standards in Relation to the Advertising of Medicines and Treatments.'"

Mr. NESS EDWARDS said that for the past two years the dentists' association had been complaining about the false claims made for certain tooth powders and that sort of thing. Had they no remedy in applying to the Postmaster-General? Mr. THOMPSON stated that the responsibility rested firmly on the Authority.

Dr. EDITH SUMMERSKILL: How does the British Code of Standards relate to proprietary drugs which are advertised and which have no therapeutic value at all? Mr. THOMPSON: All advertisements and claims for these proprietary drugs are considered by the committee and would not be approved if they were wildly extravagant.

Local Monitoring of Fall-out

Mr. R. Moss (Meriden, Lab.) asked the Prime Minister on March 5 whether he had now considered the paper on environmental radioactivity by the Coventry city analyst, read to the Warwickshire Clean Air Council; and if, in view of the anxieties expressed in the final paragraph and the facts quoted on page 5, he would take steps to have measurements of radioactivity taken locally. Mr. H. MACMILLAN stated that he had seen this paper. There was a national programme for the monitoring of fall-out. It was designed to provide reliable data for assessing the extent to which the population as a whole was exposed to fall-out. The results were published each year and did not give cause for concern. He was advised that measurements of general environmental radioactivity taken locally would not add materially to the value of these results in relation to the dangers mentioned in the paper.

Mr. Moss said that radioactivity might vary locally according to variations in local rainfall. As in the future medical officers of health might have to trace the sources of radioactive contamination, would it not be a good idea that those measurements should be taken through rainfall in co-operation with the Atomic Energy Research

Establishment? Mr. MACMILLAN said he thought the arrangements for making all these scientific calculations were very complete and gave general satisfaction to the scientists who had to study them. If Mr. Moss had any particular point to raise he would give attention to it.

Addiction to Anaesthetics

Sir FRANK MEDLICOTT (Norfolk, Central, Nat. Lib. and Con.) asked the Minister of Health on March 9 if his attention had been drawn to a recent case in which an anaesthetist involved in a fatal operation admitted at his trial that he had been addicted for seven years to inhaling anaesthetic drugs; and if he would hold an inquiry into the circumstances under which such a tendency could have been unnoticed by the hospital staffs with whom the anaesthetist had been working over this long period. He also asked if the Minister's attention had been drawn to the practice of some anaesthetists of testing anaesthetic gases by inhalation; and what inquiries he proposed to make into the extent of this practice and its effects on the capacity of anaesthetists to perform their professional duties.

Mr. D. WALKER-SMITH: I have studied with concern the proceedings in this case and am making further inquiries. I understand that many anaesthetists inhale small quantities of anaesthetic gases before administering them, and that they consider this a desirable precaution in the interests of their patients. I have asked the Committee on Drugs of Addiction, under the chairmanship of Sir Russell Brain, to consider whether any special measures are required in the light of this case.

Sir F. MEDLICOTT said there was a feeling in some quarters that medical people were reluctant to testify against each other in matters of error or negligence, and that the careful inquiries which he had instigated would possibly afford some reassurance on this very grave matter. Mr. WALKER-SMITH: I am making inquiries to seek information about the reports that were said to have been made in this particular case. In the light of that information I will consider the position in general further.

Dr. EDITH SUMMERSKILL (Warrington, Lab.): Will the Minister take into account that at the hospital where this tragic case occurred there was no medical administrator; and, although there was a medical committee with a chairman, none of the consultants on it were, of course, prepared to condemn one of their colleagues? Here is an example of the necessity to follow the Bradbeer recommendation, which said that a medical administrator should be in charge who should have overall charge and could take action in such a case as this. Mr. WALKER-SMITH: That is one consideration to be borne in mind, although it goes a good deal wider than the point under reference. The question of transmission of information does raise certain points of medical ethics which I may wish to discuss further with the profession.

Mr. HERBERT MORRISON (Lewisham, South, Lab.): As it would appear from the proceedings of the trial that it was known by some of his medical colleagues that this doctor was addicted to this kind of thing, will the Minister make sure why it was not conveyed, if it was not conveyed, to the hospital board; and, if it was conveyed, why the hospital board did not take action about it? Mr. WALKER-SMITH: I am going further into the question of the extent of the knowledge referred to in the trial, though, as I said in regard to the general position, it may be that certain questions of medical ethics arise which would require further discussion with the profession.

Migraine Treatment

Mr. READER HARRIS (Heston and Isleworth, Con.) asked the Minister of Health what proposals he had to set up under the N.H.S. clinics to deal with migraine on the lines of the Eileen Lecky Migraine Clinic at the Putney Health Centre; and what investigations had been made since July, 1954, into the work of the clinic's out-patient department. Mr. WALKER-SMITH said he was advised that the treatment available at this clinic had no advantages over that already available in the Health Service.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending February 21 (No. 7) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	2	0	3	0	1	3	0	2	0	
Dysentery	1,193	78	110	19	9	1,327	203	232	18	1
Encephalitis, acute	3	0		0		5	2		0	
Enteric fever: Typhoid	4	1	0	0	1	4	0	0	0	2
Paratyphoid	6	1	2(B)	0		2	1	2(B)	0	21 (B)
Food-poisoning	107	22	3	0		158	19	22	0	
Infective enteritis or diarrhoea under 2 years				7	31				9	18
Measles*	26,464	1561	918	648	1073	4,497	89	92	56	15
Meningococcal infection	27	2	13	1	3	42	3	10	1	4
Ophthalmia neonatorum	19	1	3	0		32	1	5	0	
Pneumonia†	2,339	265	764	10	9	882	62	336	24	7
Poliomyelitis, acute: Paralytic	10	0	1	1		13	1	4	1	3
Non-paralytic	2	0	3			5	0			
Puerperal fever§	265	53	12	1		264	42	10	3	
Scarlet fever	1,245	62	87	39	20	888	58	95	17	23
Tuberculosis: Respiratory	462	43	96	22		578	55	86	18	
Non-respiratory	47	6	5	3		82	5	12	4	
Whooping-cough	575	25	92	70	168	576	30	48	6	7

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	2	0	0	0	0
Dysentery	1	0		0		3	0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	1	0	2	13	0	3	0	1
Influenza	1,121	147	27	0	3	128	5	1	1	4
Measles		1	0	0			0	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia	1,951	259	99	25	10	944	72	41	18	8
Poliomyelitis, acute	4	0		0	0	2	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis: Respiratory	134	8	11	3	3	131	10	9	0	11
Non-respiratory		3	0	0	0		0	0	0	1
Whooping-cough	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	392	35	36	8	8	417	42	31	9	12
Deaths (excluding stillbirths)	17,143	1815	1023	153	200	13,122	929	765	151	242
LIVE BIRTHS	14,809	1235	1012	250	288	15,054	1261	1042	225	377
STILLBIRTHS	346	26	25			314	24	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Smallpox at Liverpool

A case of smallpox in a fourth-year medical student aged 21 has been confirmed at Liverpool. We are indebted to Professor A. B. SEMPLE for the following information: The patient fell ill on February 28. When the rash appeared the disease proved to be mild but typical smallpox. The patient was last successfully vaccinated in infancy. The source of the infection was not known at the time of going to press on March 10.

Influenza and Pneumonia

Numbers of deaths from influenza and pneumonia again rose in England and Wales in the week ending February 28. Influenza deaths numbered 1,571, as compared with 1,121 in the previous week, and pneumonia deaths 2,121, as compared with 1,951. Cases of pneumonia also increased (see graph) from 2,339 to 2,926, the highest weekly total for eight years.

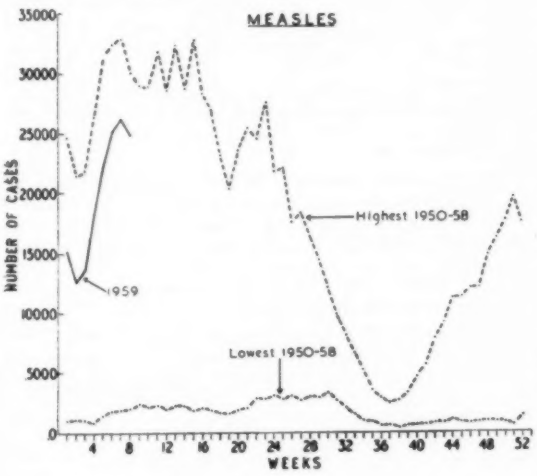
The age distribution of the influenza deaths was as follows: under 15 years, 30 (2%); 15–64 years, 421 (27%); 65 and over, 1,120 (71%). Deaths from influenza numbered 169 in Lancashire, 163 in London, 144 in Surrey, and 100 in Middlesex.

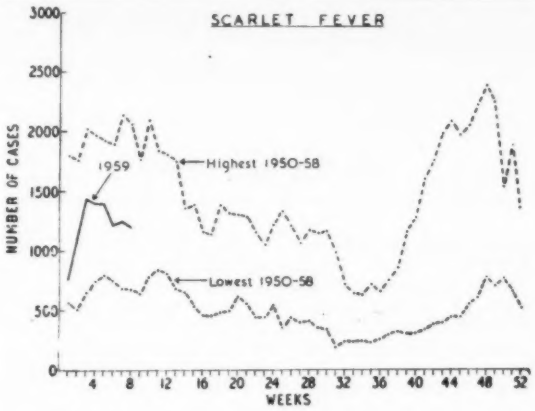
A sharp rise in the number of influenza deaths in the principal towns of Scotland was reported, from 27 to 57 in the week ending February 28. In the principal towns of Northern Ireland 4 influenza deaths were reported, and in those in Eire also 4.

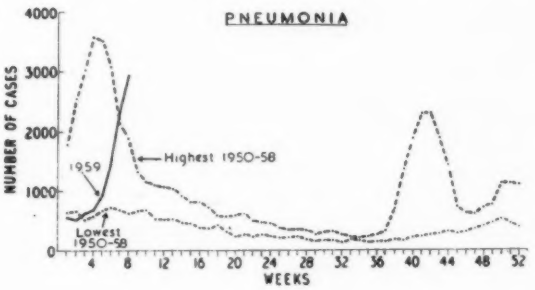
According to the Ministry of Health, influenza remains widespread in many parts of the country, though the distribution is patchy and some areas have largely escaped infection. Pressure on hospital beds has begun to ease in many areas, notably London.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Week Ending February 28

The chief fluctuations in the numbers of notifications of infectious diseases in England and Wales during the week ending February 28 were decreases of 1,513 for measles, from 26,464 to 24,951, 144 for dysentery, from 1,193 to 1,049, 38 for scarlet fever, from 1,245 to 1,207, and increases of 587 for acute pneumonia, from 2,339 to 2,926, 41 for food-poisoning, from 107 to 148, and 14 for whooping-cough, from 575 to 589.

The largest falls in the incidence of measles were 324 in Essex, from 2,747 to 2,423, 273 in Cheshire, from 948 to 675, 166 in Yorkshire West Riding, from 2,767 to 2,601, 162 in Northumberland, from 527 to 365, 156 in Middlesex, from 1,575 to 1,419, 142 in London, from 1,561 to 1,419, and the largest rises were 343 in Surrey, from 1,021 to 1,364, 226 in Warwickshire, from 1,305 to 1,531, and 136 in Staffordshire, from 704 to 840. Only small changes in the number of notifications of scarlet fever were recorded in the local returns. The largest increase in the number of notifications of whooping-cough was 34 in Warwickshire, from 12 to 46, and the largest decrease was 35 in Lancashire, from 92 to 57. Five cases of diphtheria were notified, being 3 more than in the preceding week; 3 of the cases were notified in Birmingham C.B.

Only 9 cases of acute poliomyelitis were notified during the week, and this was the lowest number for any week for almost four years. The cases were 3 fewer for paralytic and the same for non-paralytic cases as in the preceding week. Hampshire with 2 notifications was the only county with more than 1.

7 of the 11 cases of paratyphoid fever were notified in Essex, Thurrock, R.D.

The chief centres of dysentery were Lincolnshire 156 (Grimsby C.B. 82, Cleethorpes M.B. 15, Boston M.B. 14, Boston R.D. 11), Yorkshire West Riding 129 (Leeds C.B. 49, Bradford C.B. 34, Dewsbury C.B. 11), Glamorganshire 118 (Cardiff C.B. 59, Barry M.B. 26, Rhondda M.B. 22), Warwickshire 87 (Coventry C.B. 62, Birmingham C.B. 15), London 67, Lancashire 58 (Manchester C.B. 12), Middlesex

55 (Tottenham M.B. 35), Yorkshire East Riding 39 (Kingston upon Hull C.B. 30), Surrey 38 (Croydon C.B. 23), Gloucestershire 36 (Stroud R.D. 26), Northumberland 27 (Newcastle upon Tyne C.B. 10), Essex 26, and Dorsetshire 25 (Portland U.D. 25).

Medical News

Air Pollution Research. — The new Warren Spring Laboratory of the Department of Scientific and Industrial Research, which Lord HAILSHAM will open at Stevenage on June 29, is to include work on the suppression of atmospheric pollution in its initial research programme. Much of the laboratory's work will be of a chemical engineering character and will require basic engineering research to be undertaken also. The Department, in its programme of help "for researches regarded as of exceptional timeliness and promise," has made a grant to Sheffield University of more than £15,000, spread over five years, for the study of the formation and combustion of coal smoke.

Smoking in Tubes.—In a paper presented to the Royal Society of Health on March 11, Dr. L. G. NORMAN, chief medical officer of London Transport, said that in his view public opinion would gradually harden against smoking in public places until, as in some other countries, no smoking would be permitted on the Underground. He revealed that the London Transport Executive had set up an operational research team to investigate the desirability of increasing the non-smoking accommodation on tube trains from 30% to 50%.

Colonial Development Schemes.—Grants and loans totalling over £1,100,000 were made in January under the Colonial Development and Welfare Acts. Public works and health schemes accounted for nearly two-thirds of this sum. Among the grants for these schemes was £79,963 to British Guiana for the provision of cottage hospitals, health centres, and mortuaries; £62,230 to the University College of the West Indies for various construction works; and £26,000 to Sierra Leone for improvement and extension to the Connaught Hospital.

Magistrates and the Mental Health Bill. — The Magistrates' Association welcomes the procedure proposed in the Mental Health Bill for compulsory admission to hospital. It believes that both patients and the public would be better served by the new procedure than by the present system of medical and magisterial certification. This it states in a press notice dated March 6. With regard to the proceedings before the review tribunals, the Magistrates' Association hopes that these will be conducted as informally as possible, and that a patient, or his nearest relative or guardian, will have the right to call expert legal, medical, or social aid.

Safe Oysters.—The Ministry of Agriculture and Fisheries Laboratory at Burnham-on-Crouch has designed a plant for cleaning possibly contaminated oysters with the help of ultra-violet irradiation, and one has been installed at West Mersea, Essex. When, in November last year, oysters from this area were suspected of causing cases of typhoid in London (*Journal*, November 22, 1958, p. 1282), the local health authority decided that, after April 1, no oysters from a defined area were to be sold until they had been through cleansing plants approved by the Ministry of Health. Considerable work has already been done on this method of making molluscs safe to eat, both here and in Japan, but it is the first time that ultra-violet irradiation has been incorporated in cleansing tanks which are subject to the approval of the Ministry of Health.

Food Research.—Three D.S.I.R. stations concerned with the preservation, storage, handling, or protection of foodstuffs will be transferred to the Agricultural Research Council on July 1. They are the Ditton Laboratory at Larkfield, Kent, the Low Temperature Research Station at Cambridge, and the Pest Infestation Laboratory at Slough.

French Doctors' Children.—An association in Paris with offices in the "French B.M.A." tries to help the orphans and widows of French doctors by finding suitable homes in England where the children can spend some weeks in order to learn English on an *au pair* basis. These young people, between the ages of 16 and 20, could, if boys, give French lessons in exchange for hospitality, and, if girls, help with the household. British doctors who would like to enter into such an arrangement should communicate with the Association des Femmes et Enfants de Médecins, 60, Boulevard Latour-Maubourg, Paris, VII.

British Standards Institution.—A draft British Standard has been issued specifying requirements for thigh corsets and cuff tops for use with orthopaedic callipers. Comments are invited and should be sent to Mr. W. S. HODGES, British Standards House, 2, Park Street, London, W.1.

Professor G. W. Beadle, professor of biology and chairman of the division of biology at the California Institute of Technology, is to receive the honorary degree of Doctor of Science from Birmingham University in July. He is the Eastman Visiting Professor for 1958–9 in the University of Oxford, and was Nobel Laureate in Medicine for 1958.

Liquid Oxygen.—The Queen Elizabeth Hospital, Birmingham, has installed a liquid oxygen system; it will provide oxygen "on tap" in 23 wards and 9 operating theatres. Four hospitals in London are similarly equipped, one in Oxford and two in Wales.

Cambridge Science Library.—The Council of the Senate recommended on March 2 that general approval be given to the establishment of a university science library on or near one of the central laboratory sites.

Eastman Dental School.—Professor R. V. BRADLAW, dean of Sutherland Dental School, King's College, University of Durham, will succeed Dr. F. C. WILKINSON as director of studies of the Institute and director of the Hospital when he retires later in the year.

Royal Photographic Society.—Dr. W. HEWITT, Department of Anatomy, St. Thomas's Hospital Medical School, and Mr. A. L. WOODING, of the Department of Photography there, have been awarded the *Lancet* award for the best series of prints (or, in default, a single print) presented by a member of the Medical Group of the Royal Photographic Society and published in the medical press during the year 1958.

Sir Francis Walshe, F.R.S., will be in the United States during April and May, where he is to act as visiting professor of neurology in the medical schools of St. Louis, Cincinnati, and San Francisco.

Dr. Howard Nicholson, physician, University College Hospital and Brompton Hospital, London, has had the title of Fellow of University College conferred upon him by London University.

Philately.—The Falkland Islands stamp collection of Dr. D. N. NABARRO was sold on February 26 for £5,034 at Robson-Lowe's Pall Mall sale rooms. Dr. Nabarro, who died last October aged 84, was formerly consultant pathologist at the Hospital for Sick Children, Great Ormond Street. He was an acknowledged expert on the stamps of these Dependencies.

Dr. Jan Nowicki, consultant at Otwock Tuberculosis Sanatorium and chief surgical assistant at the Wolski Hospital, Warsaw, is to spend three weeks in Britain at the invitation of the British Council. Since his last visit here in 1956 he has arranged for 15 Polish doctors to receive post-graduate training in British hospitals, and he will discuss the possibility of extending these arrangements.

COMING EVENTS

B.B.C. Radio.—March 15, 9.15 p.m. Home Service: "Dr. Ernest Jones"—a portrait of the psycho-analyst assembled from the reminiscences of people who knew him.

Conference on Haematology.—This conference, organized by Glasgow University and the Royal Faculty of Physicians and Surgeons of Glasgow, will be held from March 16 to 20 at 242, St. Vincent Street, Glasgow, C.2. Details from the Registrar of the Faculty (also see *Journal*, February 7, p. 58).

National Association for Mental Health.—An annual conference on "The Place of Work in the Treatment of Mental Disorder" will be held on March 19 and 20 at the Assembly Hall, Church House, Westminster, London, S.W.1. Details from the association, 39, Queen Anne Street, London, W.1 (Tel. WEL. 1272).

Ophthalmological Society.—The Annual Congress will be held on April 9 to 11 at the Royal Society of Medicine. Details from the Ophthalmological Society of the United Kingdom, 47, Lincoln's Inn Fields, London, W.C.2.

Fédération des Sociétés de Gynécologie et d'Obstétrique de Langue Française.—18th congress, in Paris, June 15–17. Details from Dr. M. ROBEY, 4, Avenue St.-Honoré-d'Eylau, Paris, 16.

Association of Physicians of East Africa.—Annual conference in Kampala, June 18–20. Further details from Dr. P. W. HUTTON, Nakasero Hospital, P.O. Box 43, Kampala, Uganda.

NEW ISSUES

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Venereal Diseases.—Issued four times a year (£3 annually). The new issue (Vol. 34, No. 4) includes:

RECENT ADVANCES IN ANTIBIOTIC THERAPY (VTH ANNUAL SYMPOSIUM ON ANTIBIOTICS. WASHINGTON, D.C.). R. R. Willcox.
SPONTANEOUS CURE OF A POPLITEAL ANEURYSM OF SYPHILITIC AETIOLOGY. R. V. Rajam and P. N. Rangiah.
DONOVANOSIS OF THE ANUS IN THE MALE. M. Marmell.
CHRONIC BENIGN CIRCUMSCRIBED PLASMA CELL BALANO-POSTHITIS. W. Fowler.
RESULTS OF THE TREATMENT OF GONORRHOEA IN THE BIRMINGHAM CLINIC. G. Knight.
EFFECTS OF PENICILLIN, STREPTOMYCIN, AND TETRACYCLINE ON N. GONORRHOEAE ISOLATED IN 1944 AND IN 1957. A. Reyn, B. Korner, and M. W. Bentzon.
SYPHILITIC FOETUS AFTER PRENATAL PENICILLIN THERAPY. J. A. Burgess.
LYOPHILIZED SURVIVAL MEDIUM FOR THE T. PALLIDUM IMMOBILIZATION TEST. L. J Borel, R. Benteiac, and P. Durel.
SENSITIVITY OF THE T. PALLIDUM IMMOBILIZATION (TPI) TEST: A FUNCTION OF THE NUMBER OF SPIROCHAETES IN THE ANTIGEN. J. N. Miller, R. A. Boak, and C. M. Carpenter.
DIAGNOSIS OF CHRONIC PROSTATITIS. J. K. Oates.
INCIDENCE OF CHRONIC GENITAL INFECTION IN MALE PATIENTS WITH UVEITIS. R. D. Catterall.
SMALLPOX AS A CAUSE OF FALSE POSITIVE REACTIONS TO THE KAHN TEST. P. Collard and A. J. Evans.

Journal of Clinical Pathology.—Issued six times a year (£4 4s. annually). The new issue (Vol. 12, No. 1) includes:

A CRITICAL REVIEW OF HUMAN HAEMOGLOBIN VARIANTS: PART I. G. H. Beaven and W. B. Gratzer.
RENAL FUNCTION IN BURNED PATIENTS AND ITS RELATIONSHIP TO MORPHOLOGICAL CHANGES. I. G. Graber and S. Sevitt.
SOME EFFECTS ON BLOOD COAGULATION OF ERYTHROCYTES AND OTHER CELLS. J. R. O'Brien.
A TECHNIQUE FOR STUDYING THE ACTION OF ANTISEPTICS ON BACTERIA IN SUBCUTANEOUS TISSUES, WITH SPECIAL REFERENCE TO CHLORHEXIDINE. A. R. Martin.
THE BIOCHEMISTRY AND ANTIBIOTIC SENSITIVITY OF THE KLEBSIELLAE. Samuel S. Epstein.
LABORATORY INFECTION WITH TOXOPLASMA. B. D. Rawal.
CONGENITAL PULMONARY LYMPHANGIECTASIS. K. M. Laurence.
THE INCIDENCE FOUND AT NECROPSY OF METASTASES TO THE STERNUM AND ILIAC CREST WITH SPECIAL REFERENCE TO CARCINOMA OF THE LUNG. M. O. Skelton.
THE PROBLEMS OF HISTOLOGICAL DIAGNOSIS IN BASO-SQUAMOUS CELL CARCINOMA OF THE SKIN. J. Burston and R. D. Clay.
THE COLORIMETRIC ESTIMATION OF ALPHA-AMINO NITROGEN IN TISSUE FLUIDS. H. M. Rubinstein and J. D. Pryce.
A METHOD FOR THE DETERMINATION OF TARTRATE-LABILE, PROSTATIC ACID PHOSPHATASE IN SERUM. E. J. King and K. A. Jegatheesan.
TECHNICAL METHODS:
A MICRO METHOD FOR DETECTING INDOL FORMATION. Nicholas Kovacs.
THE ESTIMATION OF PROTEIN IN THE CEREBROSPINAL FLUID USING THE M.R.C. PHOTOMETER. J. G. Alexander and J. Parkes.
THE "NORMAL RANGE" OF THE PROTHROMBIN TIME ESTIMATED BY QUICK'S METHOD. G. I. C. Ineram and P. Armitage.
A SUBSTITUTE FOR THE FEULGEN STAINING TECHNIQUE. H. B. W. Greig.
THE "LAMBETH" TECHNITRAY. O. A. N. Husain.

Medical and Biological Illustration.—Issued four times a year (£3 annually). The issue (Vol. 9, No. 1), includes:

THE HAND AS AN AID TO DIAGNOSIS. Max Bürger and Hans Knobloch.
THE BUILDING AND FUNCTION OF DIORAMAS. Erik Thorn.
CONTROL OF "LITH" MATERIALS. Peter Hansell.
THE COLOURING AND MOUNTING OF BONES. J. I. H. Hadfield.
THE USE OF ULTRA-VIOLET LIGHT IN DENTAL PHOTOGRAPHY. Birgitta Lindenstam.
ELECTRONIC FLASH: A VERSATILE AND PORTABLE UNIT. Patrick M. Pawsey.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The issue (Vol. 43, No. 2), includes:

FRANCISCUS CORNELIS DONDERS. Stewart Duke-Elder.
CATARACT SURGERY. J. Barraquer and J. Boberg-Ans.
THE EYE AND RELATED GLANDS OF THE RAT AND PIG IN PROTEIN DEFICIENCY. D. S. McLaren.
ENTROPION IN HONG KONG. J. Chiao-nan Chang.
DISTENSIBILITY OF THE HUMAN EYE. J. Gloster and E. S. Perkins.
STANDARDIZED X-TONOMETERS. C. R. S. Jackson.
CHLOROMA OF THE ORBIT. S. Hameed, T. Das, and K. C. Agarwal.
VOGT-KOYANAGI SYNDROME. I. D. R. Gregory.
BIFOCAL TRIAL LENSES. J. D. Major Cardell.
OPERATION-TABLE HEAD-PILLOW. C. Montague Ruben.
NEW NEEDLE HOLDER. S. S. Sumner.

Archives of Disease in Childhood.—Issued six times a year (£4 4s. annually). The issue (Vol. 34, No. 173) includes:

THE SURGICAL IMPORTANCE OF A PERSISTENT LEFT SUPERIOR VENA CAVA. Elliott S. Hurwitt.
FUNNEL CHEST: ITS EFFECT ON CARDIAC FUNCTION. Russell Howard.
CONGENITAL ANEURYSM OF THE CORONARY ARTERY. M. Grob and E. Kolb.
LUNG HERNIA SECONDARY TO CONGENITAL ABSENCE OF RIBS. P. P. Rickham.
A SUBHYOID MEDIAN ECTOPIC THYROID. John Grieve.
PYLORIC STENOSIS BEFORE AND AFTER RAMSTEDT. Selwyn Taylor.
COMPLICATIONS AFTER OPERATION FOR OESOPHAGEAL ATRESIA. F. Rehbein and F. Yanagiswa.
RUPTURE OF THE LIVER IN THE NEWBORN. Ilse Wolfrom.
URETHRAL PLICATION IN THE MANAGEMENT OF URINARY INCONTINENCE. D. F. Ellison Nash.
BRITISH ASSOCIATION OF PAEDIATRIC SURGEONS: FIFTH ANNUAL MEETING.
A LONGITUDINAL STUDY OF THE GROWTH AND DEVELOPMENT OF PREMATURELY AND MATURELY BORN CHILDREN. PART III. MENTAL DEVELOPMENT. Cecil Mary Drillian.
THE PHYSICAL DEVELOPMENT OF MONGOLS. G. Dutton.
THE PLACE OF OATS IN THE COELIAC DIET. A. Lindsay C. Moulton.
MICROCEPHALY IN ONE OF MONOZYGOUS TWINS. M. G. W. Brandon, Brian H. Kirman, and C. E. Williams.
OXALOSIS. E. Katzum and U. Sandbank.
VISCERAL LARVA MIGRANS. W. Dickson and R. C. Woodcock.
ACUTE PELLAGRA IN A CHILD UNDER TREATMENT WITH ISONIAZID. M. G. Philpott and H. P. Player.
THE DIAGNOSTIC IMPORTANCE OF GLYCOSURIA IN LEAD POISONING IN CHILDHOOD. Ronald C. Roxburgh and Leonard Haas.
ACUTE HAEMOLYTIC ANAEMIA FOLLOWING THE INGESTION OF PARA-DICHLOROBENZENE. M. Hallowell.
THE CHILD OF THE DIABETIC WOMAN. James W. Farquhar.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, March 16

●HUNTERIAN SOCIETY.—At Talbot Restaurant, London Wall, E.C., 7 for 7.30 p.m., dinner meeting. 8.30 p.m., discussion: The Emergence of Industrial Medicine. To be opened by Dr. L. G. Norman and Dr. R. S. F. Schilling.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor T. B. Counihan: Treatment of Cardiac Oedema.

Tuesday, March 17

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Mr. J. G. Bonnin: Cysts of the Menisci.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. C. M. Ridley: Dermabrasion.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. M. O. Skelton: Some Pathological Lesions of the Adrenal Gland.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. Aleck Bourne: Clinical Significance of Amenorrhoea.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Mr. R. J. V. Battle: Cleft Lip and Palate.

Wednesday, March 18

EUGENICS SOCIETY.—At Rooms of Royal Society, Burlington House, Piccadilly, W., 5.30 p.m., Dr. R. W. Parnell: Physique and Family Structure.
FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.30 for 4 p.m., Frederic Hewitt Lecture by Dr. C. Langton Hewer: Forty Years On.
HARVEIAN SOCIETY OF LONDON.—8.15 p.m., Harveian Lecture by Professor E. B. Chain, F.R.S.: Recent Studies in Carbohydrate Metabolism.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. T. Ingram: Seborrhoeic Diathesis.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. S. Plummer: Pulmonary Tuberculosis Before Chemotherapy.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. G. Hanley: Tuberculous Infections of the Urinary Tract.
MIDLAND MEDICAL SOCIETY.—At the General Hospital, 8.15 p.m., clinical meeting.

NORTH-WESTERN THORACIC SOCIETY.—At Aintree Hospital, Liverpool, 5 p.m., Dr. R. G. Williams: Dual Reading of Miniature Films. Mr. Leslie Temple: Surgery of Pulmonary Tuberculosis—Experience since 1950.

PLYMOUTH MEDICAL SOCIETY.—3 p.m., visit to the Royal Institution, Starcross.

POSTGRADUATE MEDICAL SOCIETY OF LONDON.—2 p.m., Professor J. W. Howie: Steam Sterilization.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4 p.m., Frederic Hewitt Lecture by Dr. C. Langton Hewer: Forty Years On.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. H. K. Snell: Work of the Prison Medical Service (illustrated).

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Dr. Valy Menkin (Philadelphia): Biochemical Mechanisms Involved in Inflammation.

WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.45 p.m., Presidential Address by Mr. F. W. M. Pratt: Intussusception.

Thursday, March 19

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Dr. D. A. Wilson: Some Health and Safety Problems.

FOUNTAIN HOSPITAL.—5.30 p.m., subject: Treatment of Phenylketonuria. Papers by Dr. L. I. Woolf, and Drs. C. M. B. Paré, M. Sandler, and R. S. Stacey.

HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., symposium: Hypnosis in Surgical and Dental Anaesthesia. Speakers, Mr. M. Susman and Mr. E. E. Wookey. Film by Dr. D. Kelsey. A discussion will follow.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., annual meeting. Election of president and officers. Followed by ordinary meeting. Mr. K. W. Monsarrat: The British Hospital Service, Past and Present; Dr. T. Lloyd Hughes: Administrative Problems of the Present National Health Service.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 8 p.m., Dr. G. J. C. Brittain: Use of the Post-operative Recovery Ward.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At Royal Army Medical College, Millbank, S.W., 7.30 p.m., laboratory meeting.

Friday, March 20

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, South Parks Road, Oxford, 11 a.m., 381st meeting.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—(1) 3.30 p.m., clinical discussion for general practitioners. Mr. W. McKenzie: Advances in the Treatment of Deafness. (2) 5.30 p.m., Dr. A. C. Thackray: Salivary Gland Tumours of the Palate.

LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.45 p.m., Mr. Stuart Mawson: Becoming a Christian.

●ROYAL INSTITUTION.—9 p.m., Air Commodore W. K. Stewart, R.A.F.: Man as a Controller of Flight Vehicles.

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Hospital for Sick Children, 8.30 p.m., clinical night.

Saturday, March 21

ASSOCIATION OF CLINICAL BIOCHEMISTS.—At Department of Biochemistry, South Parks Road, Oxford, 10.30 a.m., joint meeting with Biochemical Society. Scientific papers, including symposium on Biochemical Aspects of Hereditary Metabolic Diseases. 4.30 p.m., general meeting.

●CAMBRIDGE UNIVERSITY POSTGRADUATE MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, symposium on Hypothermia. *Morning Session*, 10.30 a.m., Dr. W. R. Keatinge and Dr. G. R. Graham: Physiology of Hypothermia. *Afternoon Session*, 2.30 p.m., Dr. Ian C. W. English: Hypothermia in Cardiac Surgery. Dr. Sheila M. Anderson: Use of Hypothermia in Neurosurgery.

ILEOSTOMY ASSOCIATION OF GREAT BRITAIN: LONDON DIVISION.—At B.M.A. House, Tavistock Square, W.C., 2.30 p.m., Mrs. B. R. Stanton and Dr. F. Avery Jones: Diet and Ileostomy.

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Maidstone Technical School for Girls, Albion Place, Maidstone, 3 p.m., Presidential Address by Dr. Wilfrid Sheldon: Difficult Children.

Sunday, March 22

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, symposium. 2 p.m., Dr. D. McC. Gregg: Use of Contrast Media in *X*-ray Diagnosis; 2.45 p.m., Mr. A. S. H. Walford: Ear in General Practice; 3.45 p.m., Dr. A. P. Dick: Chronic Diarrhoea; 4.30 p.m., Dr. E. M. Cheffins: Pulmonary Tuberculosis—The Present Position.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—J. G. Hoult, M.B., Ch.B., D.C.H., D.Path., Whole-time Consultant Pathologist to Birmingham (Dudley Road) Group of Hospitals; J. R. Mathers, M.B., Ch.B., D.P.M., Whole-time Consultant Psychiatrist and Medical Superintendent to Rubery Hill Hospital, Birmingham; W. I. H. Bourne, M.B., Ch.B., D.M.R.D., Part-time Consultant Radiologist (nine notional half-days weekly) to the West Bromwich Group of Hospitals; J. S. Cason, M.B., Ch.B., F.R.C.S.Ed., Whole-time Consultant Surgeon to the Burns Unit Birmingham Accident Hospital; H. R. Thomson, M.D., M.R.C.P., Whole-time Consultant Physician (Geriatrics) to the Coventry Group of Hospitals; R. P. Matthews, M.B., B.S., Whole-time Senior Casualty Officer to the South Worcestershire group of hospitals.

BRIGHTON COUNTY BOROUGH.—Gladys M. G. Spencer, M.R.C.S., L.R.C.P., D.P.H., and P. M. Browne, M.R.C.S., L.R.C.P., D.P.H., Senior Assistant Medical Officers (from April 1, 1959).

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Jean E. Drake, M.B., B.S., D.C.H., and M. K. Strelling, M.B., B.S., D.C.H., House-physicians; J. L. Castle, M.B., B.S., F.R.C.S., and M. J. Hawken, M.B., B.S., House-surgeons; S. J. Cohen, M.B., B.Ch., F.R.C.S., M.R.C.P.Ed., Resident Assistant Surgeon; Therese M. Vanier, M.B., B.Chir., Assistant Medical Registrar; J. P. Partridge, M.B., B.S., F.R.C.S., Surgical Out-patient Assistant; T. McKendrick, M.B., B.S., M.R.C.P., D.P.H., D.C.H., Medical Registrar and Pathologist; Patricia Painter, M.B., B.S., F.F.A. R.C.S., D.A., Resident Anaesthetic Registrar; I. B. Houston, M.B., Ch.B., M.R.C.P., and W. C. Marshall, M.B., B.S., D.C.H., House-physicians; J. D. Atwell, M.B., Ch.B., Primary F.R.C.S.Ed., House-surgeon.

LIVERPOOL REGIONAL HOSPITAL BOARD.—S. D. McAusland, M.D., D.A., Part-time Consultant Homoeopathic Physician, giving two sessions per week to Liverpool Homoeopathic Hospital; R. R. Steinert, M.R.C.S., L.R.C.P., D.P.M., Whole-time Assistant Psychiatrist at Winwick Hospital; A. S. Davidson, M.B., Ch.B., F.R.C.S.Ed., D.L.O., Part-time Consultant Otorhinolaryngologist, giving eight sessions per week to St. Helens, Ormskirk, Widnes, and Runcorn Areas; Edith M. McConnell, M.D., Consultant Pathologist, giving maximum part-time sessions to the South Liverpool Group and at Liverpool Radium Institute; R. N. Sidebotham, M.B., B.S., F.F.A. R.C.S., D.A., Part-time Consultant Anaesthetist, giving eight sessions per week in Southport and North Liverpool Group; J. H. E. Carmichael, M.D., D.M.R.D., Part-time Consultant Radiologist at Broadgreen and Newsham General Hospitals; I. M. Morrison, M.B., Ch.B., F.R.C.S., Part-time Consultant Assistant Thoracic Surgeon, Regional Thoracic Surgery Service.

MANCHESTER REGIONAL HOSPITAL BOARD.—J. G. Stewart, M.B., Ch.B., F.F.R., D.M.R.T., Whole-time Consultant Radiotherapist, Christie Hospital and Holt Radium Institute; J. E. Dalby, M.B., B.Chir., D.M.R.T., Whole-time Assistant Radiotherapist (S.H.M.O.), Christie Hospital and Holt Radium Institute; T. A. Harper, M.B., B.S., Whole-time Assistant Pathologist (S.H.M.O.), South Manchester Group of Hospitals; K. L. Barnes, F.R.C.S., F.R.C.S.Ed., Maximum Part-time Consultant Orthopaedic Surgeon and Surgeon Superintendent, Wrightington Hospital, near Wigan; A. M. Womack, M.B., Ch.B., M.R.C.P.Ed., D.Path., Whole-time Consultant Group Pathologist, Bury and Rossendale Hospital; P. Crosby, M.B., B.S., M.R.C.P.Ed., D.T.M.&H., Whole-time Assistant Chest Physician, Nab Top Sanatorium Marple, Cheshire, and associated Chest Clinics; G. M. Gibb, M.B., Ch.B., D.P.M., Whole-time Consultant Psychiatrist and Deputy Medical Superintendent, Lancaster Moor Hospital.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Clare.—On March 2, 1959, to Mary, wife of Deryck E. Clare, M.B., B.S., D.P.H., of "Rose Dene," Berry Hill, near Coleford, Glos, a brother for John and Geoffrey.

Fear.—On March 1, 1959, at Harrogate General Hospital, to Jean, wife of Dr. Eric C. Fear, a daughter.

Flynn.—On February 25, 1959, at University College Hospital, to Ann (formerly Warrick), wife of Dr. Frederick V. Flynn, a daughter.

Ingall.—On March 2, at Scaurbank, Longtown, Cumberland, to Dr. and Mrs. George Ingall, a son—Paul.

Neville.—On March 2, 1959, at Queen Charlotte's Hospital, to Ruth (formerly Wood), wife of Dr. R. Neville, a brother for Susan—Stephen.

Turner.—On March 5, 1959, to Helen Mary, wife of Dr. Winston Turner, of "Bodnant," Keighley Road, Colne, Lancs, a sister for Judy and Mark—Claire Helen.

DEATHS

Bates.—On February 20, 1959, Joah Lyon Bates, M.B., B.S., M.R.C.P., D.P.M., D.C.H., of Wood Lea, Peppard Common, Henley-on-Thames, Oxon.

Beattie.—On February 22, 1959, at Greenholm, Callander, Perthshire, Alfred Jordan Beattie, M.B., Ch.B.

Costobadie.—On February 14, 1959, at Singmore Farm, Stover, Newton Abbot, Devon, Vincent Ackroyd Palliser Costobadie, F.R.C.S.Ed., D.O.M.S.

Finkel.—On February 22, 1959, Salomon Finkel, M.D., of Great Houghton, near Barnsley, Yorks.

Gunter.—On February 9, 1959, Herbert Charles Robert Gunter, M.D., D.A., of Crescent House, Billericay, Essex.

Houghton.—On February 21, 1959, in North Wales, the result of a climbing accident, Eric Alfred William Houghton, M.B., Ch.B., of Nailsea, Somerset, aged 31.

Hughes.—On February 15, 1959, at his home, Y Wern, Llanfairfechan, Caerns, Lloyd Hughes, M.B., Ch.B., aged 74.

Kelly.—On February 26, 1959, in hospital, Simon Kelly, M.B., Ch.B., M.R.C.P., D.P.M., D.P.H., aged 60.

King.—On February 18, 1959, at Newton Abbot Hospital, Colin King, O.B.E., M.B., F.R.C.S.Ed., of Brinckley Lodge, Newton Abbot, Devon.

Kirkwood.—On February 21, 1959, at Frenchay Hospital, Bristol, William Kirkwood, M.B., Ch.B., of 66, Wallscote Road, Weston-super-Mare, Somerset, aged 54.

Livingston.—On February 3, 1959, at Glenacres, Dunblane, Perthshire, John Henderson Bruce Livingston, T.D., M.B., Ch.B.

Lynch.—On February 3, 1959, at Cork, Eire, Eileen Lynch (formerly McConnon), M.B., B.Ch., formerly of Bradford, Yorks, and Manchester, Lancs.

McDonald.—On February 25, 1959, at Goudhurst, Kent, Donald Percy McDonald, M.B., F.R.C.S.Ed., Lieutenant-Colonel, I.M.S., retired, late of Littlehampton, Sussex.

McKenna.—On February 9, 1959, at 238, Manley Road, Chorlton-cum-Hardy, Manchester, Patrick McKenna, L.R.C.P.&S.I. & L.M., aged 57.

Manderson.—On February 18, 1959, at 311, Ewell Road, Surbiton, Surrey, Mungo Manderson, M.B., Ch.B., formerly of Glasgow, aged 57.

Mills.—On February 20, 1959, at his home, 47, Blandford Road, Corfe Mullen, Wimborne, Dorset, Horace Macaulay Mills, M.B., Ch.B.

Robertson.—On February 21, 1959, at Corrennie, West Kilbride, Ayrshire, David Gordon Robertson, M.B., Ch.B., late of Polmont, Stirlingshire.

Slater.—On February 24, 1959, at Scarborough Hospital, Benjamin Holroyd Slater, M.B., F.R.C.S., of Lastingham, York, formerly of Bradford, Yorks.

Snowman.—On February 28, 1959, at 14, Briardale Gardens, London, N.W., Jacob Snowman, M.D., M.R.C.P., aged 87.

Steele.—On February 9, 1959, Russell Vyvyan Steele, M.B., B.S., of Penrhyn Lodge, Gloucester Gate, London, N.W., aged 70.

Stephens.—On February 18, 1959, Horace Elliott Rose Stephens, O.B.E., M.B., F.R.C.S., D.P.H., Surgeon Rear-Admiral, R.N., retired, of Gwynfa, Trearddur Bay, Anglesey, aged 76.

Taylor.—On February 15, 1959, at Walton-on-Thames, Surrey, Emma Taylor, L.R.C.P.&S.Ed., L.R.F.P.S., aged 95.

Thomas.—On February 23, 1959, Ivor Elwyn Joseph Thomas, M.D., M.R.C.O.G., of Pembury, Kent, aged 45.

Turner.—On February 22, 1959, at his home, Fairford, Glos., Arthur Charles King Turner, M.B., C.M.

Walker.—On February 19, 1959, at 10, Gunton Cliff, Lowestoft, Suffolk, Robert Lawrence Walker, M.B., B.S., aged 62.

Walmsley.—On February 5, 1959, at the National Hospital, London, W., William Claud Dudley Walmsley, M.B., Ch.B., D.P.H., of Ingleside, Odiham, Hants.

Walters.—On February 16, 1959, at Chiswick House, Pinner, Middx, Hubert Walters, M.R.C.S., L.R.C.P., aged 37.

Wight.—On February 15, 1959, at Hove Hospital, Edward Wight, M.R.C.S., L.R.C.P., of 19, York Avenue, Hove, Sussex, aged 79.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Pain in Pancreatitis

Q.—*What is the aetiology of the pain in chronic pancreatitis and what is the most effective way of controlling it?*

A.—The condition referred to is probably the relapsing form of subacute pancreatitis in which the pain is more intractable than it is in a true chronic pancreatitis. The mechanism of the pain is not completely determined, but the fact that it may be worsened by morphine suggests the possibility of an element of duct obstruction. In addition, however, the areolar tissues surrounding the pancreas are sometimes found at operation to be oedematous, and this too contributes to the pain. Furthermore, any pain which is referred to the left shoulder tip is due to irritation, arising in this way, of the terminal filaments of the phrenic nerve innervating the peritoneum of part of the lesser sac. The local boring pain, which may be referred around the trunk to the costo-vertebral angle posteriorly, is likely to be of sympathetic origin. It must be remembered that the gland is in immediate relationship with the large plexuses and ganglia of the upper abdominal sympathetic innervation.

The pain of chronic or subacute pancreatitis is notoriously unyielding to the usual remedies. As mentioned above, morphine and its derivatives frequently fail to relieve it and may even make the pain worse, so that other analgesic drugs have to be employed despite the knowledge that they fall short of morphine in their central effects. There are many of the newer synthetic analgesics which may be used, but experience shows that it is usually necessary to find which best suits any particular case by the method of trial and error. Whichever is chosen, it should be combined with one of the antispasmodic drugs—atropine and its derivatives—or some of the synthetic antispasmodics now available. In more severe cases, when these measures fail, injection of the splanchnic nerves with alcohol or phenol by the usual technique (Kappis) is advised. This, of course, can alleviate only that element of the pain which the sympathetic subserves, but may nevertheless be sufficiently rewarding. Finally, leucotomy has been employed in the most intractable cases. The writer, however, is of opinion that a laparotomy should first be done to see if any local measure, possibly even a pancreatectomy, might not give more direct relief.

Chlorpromazine in Asthma

Q.—*Has chlorpromazine been shown to be of value, orally or parenterally, in the treatment of asthma? Is there any contraindication to its use?*

A.—The effects of chlorpromazine in asthma are variable. Michelson and Lowell,[1] in a controlled study of seven asthmatics given 15–25 mg. chlorpromazine intravenously in 250 ml., found no consistent subjective relief or evidence of a bronchodilatation effect by closed-system spirometry, although sedation was marked. Two asthmatics had increased symptoms immediately after the infusion and then were rapidly improved with intravenous aminophylline.

Renzetti and Padget,[2] from careful studies in seven normal and two emphysematous patients given 25 mg. intravenously, suggested that chlorpromazine had a respiratory depressant action. In one subject the blood pressure fell to unobtainable levels, and they point out the potential hazard of the intravenous route for therapeutic use. Baum *et al.*,[3] in ten uncomplicated asthmatics given 25 mg. intravenously, found a marked diminution of wheezing and restlessness in five, with no relief in two, and in the remainder the chlorpromazine was combined with conventional bronchodilatation therapy. In six patients with asthma and emphysema, distinct lessening of the dyspnoea was noted in one subject. Similar benefit occurred in two when the drug was combined with conventional bronchodilatation therapy. Aminophylline-induced vomiting was alleviated in one. In two patients there was no relief of dyspnoea, both of whom were subsequently relieved by corticotrophin.

Chlorpromazine can be recommended parenterally only in severe asthma as an adjuvant, and care must be taken to counteract the occasional marked fall in blood pressure which may occur, especially if it is given intravenously. Orally, as a prophylactic between attacks, its effect is again somewhat disappointing. In a few patients the attacks appear to be reduced, but not infrequently the patients describe themselves as feeling better but that the attacks themselves have not been affected. Tuft's[4] experience is that chlorpromazine and other tranquillizing agents given by mouth did not help asthmatic children, even those with behaviour problems.

REFERENCES

1 Michelson, A. L., and Lowell, F. C., *Amer. J. med. Sci.*, 1957, **234**, 31.
2 Renzetti, A. D., and Padget, W. R., *J. Lab. clin. Med.*, 1957, **50**, 400.
3 Baum, G. L., Schotz, S. A., Gumpel, R. C., and Osgood, C., *Dis. Chest*, 1957, **32**, 574.
4 Tuft, L., *Ann. Allergy*, 1958, **16**, 481.

Survival of Premature Babies

Q.—*Is there any justification for the belief, held in certain parts of the world, that a baby born prematurely in the 8th month is less likely to survive than one born in the 7th month?*

A.—The figures available from centres in this country specializing in the care of premature infants support the more reasonable belief that the longer the gestational period the better the chances for survival in a premature baby. However, the effect of basing an international definition of prematurity upon birth weight is that babies approximating to 5½ lb. (2.500 g.) may be regarded as small mature infants, while those weighing 3–4½ lb. (1,360–2.040 g.) are given the special care required by premature infants. In this way some of the less fortunate eight-month babies may succumb through their functional immaturity, whereas the seven-month brothers are receiving considerable prophylactic care and attention.

Hormones and Physique

Q.—*What hormonal or other factors are responsible for the bony skeleton of some adolescent females becoming broad, short, and heavy, with markedly broad pelvis and hips, especially in the absence of obvious hereditary factors? Is there any known method of prevention or modification?*

A.—The hormonal and other factors underlying the differential growth to produce one type of physique rather than another are not at all understood at the present time. The growth of the female pelvis is specifically stimulated by the oestrogen secreted at puberty, but it does not appear that these hormones act on the rest of the bony skeleton in the dose in which they are produced normally. The two hormones which, on rather vague grounds, would usually be considered as possibly causing the skeleton in general to become broad, short, and heavy would be either growth hormone or androgens, but any such opinion at the moment would be very speculative.

Prolonged Use of "Pregnyl"

Q.—*I have been using injections of pregnyl with good effect in treatment of migraine. Might its prolonged use over several years cause neoplasms of the female reproductive organs or cause heavy periods?*

A.—The use of pregnyl (chorionic gonadotrophin) in migraine has been recommended by several authors, whereas others have denied its efficiency. Theoretically it might be useful in the premenstrual type of migraine by stimulating the production of corpora lutea and thus of progesterone (which is highly effective in most cases). It is more likely

that those who praise it are giving to one part of their treatment the credit really owed to their general good doctoring. However this may be, there is no evidence to suggest that its prolonged use is likely to lead to neoplasms of the female reproductive organs or to menorrhagia.

Risk of Tetanus

Q.—*What is the risk of developing tetanus if A.T.S. is not given compared with the risk of a severe reaction if A.T.S. is given?*

A.—The chances of tetanus developing after an injury increase with the following conditions: (1) punctured, lacerated, crushed, or multiple wounds; (2) contamination with soil, dirt, or manure; and (3) the prevalence of tetanus in the locality—a prevalence existing naturally on all agricultural lands. The chances of a severe reaction after A.T.S., when administered with the proper precautions, would be very small. These precautions have been described by Laurent and Parish.[1] The trial dose should be 0.2 ml.; the interval between the trial dose and the full dose should not be less than 30 minutes. An injection of 1 ml. of 1 in 1,000 adrenaline and a bed or couch for the patient to lie on should always be in readiness in case of allergic shock. But would it not be wiser to immunize against tetanus those especially at risk to it?[2]

REFERENCES

[1] Laurent, L. J. M., and Parish, H. J., *Brit. med. J.*, 1952, 1, 1294.
[2] Parish, H. J., Laurent, L. J. M., and Moynihan, N. H., ibid., 1957, 1, 639.

Green Fluorescence in Urine

Q.—*What is the cause of a green fluorescence in freshly or nearly freshly voided urine?*

A.—Green fluorescence in fresh or nearly fresh urine is most commonly of dietary origin, the usual material responsible being the dyestuffs of cheap sweets. A yellowish-green fluorescence, however, is sometimes observed after vitamin preparations containing large quantities of riboflavin.

NOTES AND COMMENTS

Cold Storage of Blood.—OUR EXPERT writes: In the question and answer headed "Cold Storage" ("Any Questions?" February 14, p. 453) there was an error in the description of the storage conditions for whole human blood. The *British Pharmacopoeia* directions for the storage of this and of concentrated human red blood corpuscles are that they are to be kept in sterile containers, sealed so as to exclude micro-organisms, and stored at a temperature of 4–6° C. Whole blood may be removed from cold storage for short periods for examination or transportation at higher temperatures, but any such period must not exceed 30 minutes, after which the blood must immediately be cooled again to 4–6° C. Concentrated human red blood corpuscles must be used not more than 12 hours after preparation. Apart from the above, and injection of human gamma globulin which has a storage temperature of 2–4° C., the remaining official blood products must be stored at a temperature below 20° C.

Ringworm.—Dr. J. MARTIN BEARE (Belfast) writes: May I be permitted to write in support of your expert's answer to the question on ringworm ("Any Questions?" December 6, 1958, p. 1424) and his reply ("Notes and Comments," January 31, p. 316) to the letter received from Drs. A. Girdwood Fergusson and W. A. Dewar? It should be noted that the times for cure without *x*-ray epilation of *M. canis* scalp infection given by Drs. Fergusson and Dewar (31 to 81 days for seven inflammatory cases and 50 and 67 days for two non-inflammatory cases) show clearly that *M. canis* does not behave differently in the west of Scotland from either your expert's territory or mine (both under three months—with the rare exception). One cannot justifiably add the duration of infection before the case is seen to the non-epilated case without also adding it to the epilated case, so in practice we must deal only with the known average duration of infectivity after the case is seen. Undoubtedly an epilated child will be clear in three to four weeks, but bald for another two to three months, and socially unacceptable in the case of a girl for as much as a year. That alone gives rise to very considerable emotional troubles in young children. The worry about the potential risks of *x*-ray epilation ("near the danger line for the skin," and perhaps of no small genetic importance too) is something which I am sure is shared by all of us, including Drs. Fergusson and Dewar. The only reason for treating this symptomless affection with *x* rays at all is the danger of spread of infection to other children. This is considered by all to be a justifiable reason when dealing with *M. audouini* infections. My own experience would indicate that tinea capitis due to *M. canis* is, from a practical point of view, not infectious to other children. In other words, the great majority of children are infected from kittens and dogs (especially kittens) and the important thing in preventing epidemics is to find and destroy the infected animal(s). Meantime the infected children can go to school with a cover of some greasy ointment and advice not to take part in group games. I would suggest, Sir, that if Drs. Fergusson and Dewar would forget their children with *M. canis* infections and go on a cat-hunting expedition (for about three months) they would find on their return no further reason to use *x*-ray epilation for this condition.

Post-operative Pain.—Dr. I. M. CULLUM (Spalding) writes: I am surprised that no mention was made of heroin in the reply to the question regarding allergy to morphine ("Any Questions?" January 17, p. 186). I write as one who is extremely sensitive to morphine, "omnopon," and pethidine, a single dose of any of these substances causing the most intense giddiness, headache, and vomiting for approximately 12 hours. These highly unpleasant side-effects do not follow heroin, and the relief afforded me by a single dose has been so dramatic on two separate occasions following surgical intervention that I am convinced that heroin should remain in our therapeutic armamentarium. If oral medication can be tolerated, codeine is also useful for less severe pain.

OUR EXPERT replies: It is true that heroin is less likely to cause nausea and vomiting than morphine. The danger of addiction to this drug is great, and it is not usually the best second choice in cases in which morphine causes unpleasant side-effects. The use of heroin may, however, be justified in an individual patient if it has been found by experience that alternative analgesics give rise to nausea and vomiting. It is essential that it should be used only over short periods of time, but this is usually the case in dealing with post-operative pain. Codeine is a relatively ineffective analgesic and must be given in a dose of 60 mg. (1 gr.) for the relief of pain. It is safe and non-addicting and does not usually cause vomiting, but it gives rise to constipation which may be severe.

Hangover.—Dr. R. M. BADDELEY (Chesterfield) writes: The treatment of hangover ("Any Questions?" January 24, p. 248) is such a common minor problem that it is surprising that more attention has not been paid to it. In the absence of a specific remedy I have observed that the "morning after" becomes much more bearable with codein. co. 10 mg., mist. mag. trisil. 1 fl. oz. (28 ml.), and dexamphetamin. sulph. 5–10 mg.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Emergencies in General Practice (26s. 9d.).

Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

Clinical Pathology in General Practice (22s. 3d.).

Any Questions?, Volumes 2 and 3 (8s. 3d. each).

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the ASSOCIATION. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.